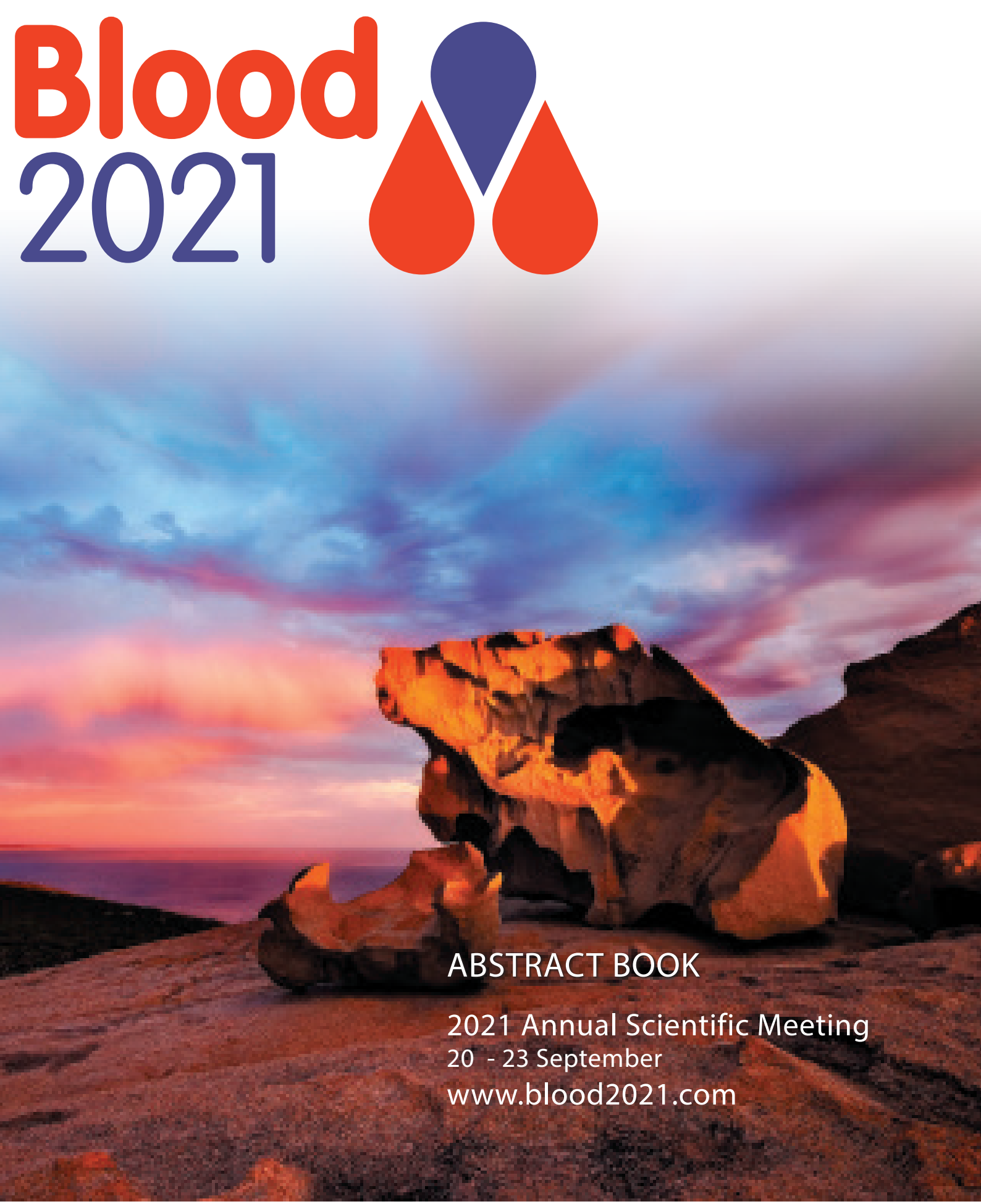
Blood 2021



ABSTRACT BOOK

2021 Annual Scientific Meeting

20 - 23 September

www.blood2021.com

The combined Annual Scientific Meeting of the:

HSANZ Haematology Society of Australia and New Zealand

ANZSBT Australian & New Zealand Society of Blood Transfusion Ltd

THANZ Thrombosis & Haemostasis society of Australia and New Zealand

Contents

1. Oration Abstracts

Barry Firkin Oration: The future of oral anticoagulant therapy

Prof John Eikelboom

Despite remarkable advances in anticoagulant therapy over the past 3 decades, unmet needs remain. Currently available anticoagulants produce variable anticoagulant effects, the newer agents are unsuitable for patients with advanced kidney disease, and they are all associated with a significant risk of bleeding. New approaches that target the contact pathway of coagulation (e.g., factor XIa, XIIa) or upstream drivers of coagulation activation (e.g., inflammation, NETS, CHIP) have the potential to improve safety and ease of use, and further expand the use of anticoagulants to prevent morbidity and mortality due to thromboembolism.

Ruth Sanger Oration: From Florence to patient blood management: the evolution of transfusion nursing roles

Mrs Linley Bielby
Blood Matters Program Manager, Department of Health and Australian Red Cross Lifeblood, Victoria
(Dip App Sc, BN (Maj Ed), Grad Dip Health Counselling, Grad Dip Transfusion Practice, MHA)

Florence Nightingale (1820-1910), is known as “The Lady with the Lamp”. A professional pioneer, social reformer and statistician, she is best known today as the founder of modern nursing. Not only did she leave a formidable legacy to nursing and healthcare more generally, we have her to thank for introducing professional nursing to Australia.

Since those early days, we have seen nursing evolve and specialise, with specialist nursing roles in transfusion and blood management introduced in Australia and New Zealand in the early 2000s. These roles build on Florence’s foundation of ‘do no harm to the sick’, and her examples of collecting and using data to provide evidence for change, and supporting improved practice continue today. Now central to transfusion clinical practice, it’s hard to imagine a time before this important role existed. Being educators, auditors, change agents and researchers are but a few of the hats we wear…

Specialist transfusion/blood management nursing roles are an important part of the modern multidisciplinary blood sector, with a vast network both nationally and internationally. Our mantra of striving for best practice supports Florence’s quote “Were there none who were discontented with what they have, the world would never reach anything better” (Cassandra: an Essay (1860) part 2.).

Carl de Gruchy Oration – Being Fearless

A/Prof Bryone Kuss

Our world requires fearless people. We need fearless research, fearless advocacy, fearless defenders. Doctors are fearless researchers and fearless advocates for their patients, but they are rarely fearless defenders of themselves. There is more stress and anxiety in this technology intense world than ever before, yet despite living in a Global pandemic with outstanding achievements in vaccine technology, the governing world continues to focus on ego and militancy.
The Carl de Gruchy oration provides me with the opportunity to present our work in Chronic Lymphocytic Leukaemia and to discuss the ongoing utility of single case exploration, when sharp minds ask probing questions. Also, the emerging role of techniques beyond genomics that will drive research, creating new opportunities for fundamental understanding of lymphoproliferative diseases and their remedies. I will also utilise this time to showcase the incredibly talented women in our society of haematologists, demonstrate their fearlessness and present evidence that haematology in Australasia is leading the way for strong female directorship. I wish to context this within fearlessness, with the hope that this encourages the mentoring of our young fearless emerging stars, bringing them onto the international stage.

2. Combined Sessions

COVID19 Convalescent Plasma/Hyperimmune Ig

Professor Erica Wood

Convalescent plasma is collected from donors recovered from an infection and whose plasma contains therapeutic antibodies against an agent of interest. It can be collected by apheresis or by separating plasma from whole blood donations. Convalescent plasma offers the potential to deliver immediate passive immunity before a specific infection prophylaxis or therapy is available, and has been used with variable success for over a hundred years. It can be available early in a disease outbreak, is widely accessible, and relatively affordable, and can be transfused as clinical plasma or used for further manufacture of a polyclonal hyperimmune immunoglobulin.

Convalescent plasma for SARS-CoV-2 infection and COVID-19 disease is very topical, and results from some large trials have recently been published and/or shared in pre-print.

This presentation addresses the rationale for use of convalescent plasma and hyperimmune immunoglobulin; some aspects of collection, preparation and testing; evidence for their clinical use in the setting of COVID-19; and some considerations for future research. Some of the challenges in designing, undertaking and interpreting the results of recent studies, both randomised and non-randomised, will be discussed. Several aspects of this presentation are based on experience from Australia/New Zealand and internationally of participating in these trials (such as ASCOT and REMAP-CAP), and recent reviews which provide additional details (please see references).

References:

- *Wood EM, Estcourt LJ, McQuilten ZK. How should we use convalescent plasma therapies for the management of COVID-19? Blood. 2021;137(12):1573-1581*
- *Piechotta V, Iannizzi C, Chai KL, Valk SJ, Kimber C, Dorando E, Monsef I, Wood EM, Lamikanra AA, Roberts DJ, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021;5(5):CD013600.*

From NATA to FACT accreditation – The Fiona Stanley Hospital experience

Ms Celeste Hill & Mrs Clair Scott

Case-study:

Fiona Stanley Hospital in Western Australia was commissioned in 2015, migrating the existing WA Adult Allogeneic Transplant Program to its new facilities becoming the Fiona Stanley Hospital Blood and Marrow Transplant Program. The apheresis collection facility and onsite bone marrow transplant laboratory were accredited by NATA in 2016, followed by the Program embarking on the journey to obtain accreditation by the Foundation for the Accreditation of Cellular Therapy (FACT).

Significant planning, change implementation and multi-disciplinary engagement and teamwork was involved in preparing for the rigorous international accreditation process. Celeste and Clair are grateful for the opportunity to describe the centre's experience from a quality, laboratory and apheresis nursing perspective including the unique challenges and benefits experienced throughout the process of becoming the second FACT Accredited adult allogeneic transplant program in Australia.

New approaches to the challenges of adult and elderly Acute Lymphoblastic Leukaemia

Dr Shaun Fleming

Acute lymphoblastic leukaemia (ALL) remains a significant challenge in adult patients. While often considered a disease of children, just under half of patients will be diagnosed as adults, and the burden of relapsed disease and death from ALL overwhelmingly lies with adult patients, with elderly patients having a dismal prognosis with ALL. Adult patients with ALL have a distinctly different genomic landscape of disease with higher rates of receptor tyrosine kinase driven ALL (both Ph-positive (Ph+) and Ph-like disease), with significantly lower rates of favourable prognostic disease. This adverse risk profile is further compounded by their increased vulnerability to therapy with increased treatment related mortality seen in adults over the age of 55.

New approaches to ALL therapy are helping to bridge this gap. In younger adults the advent of paediatric-inspired regimens has bridged some of the gap with paediatrics. The impact of tyrosine kinase inhibitors (TKI's) on Ph+ disease have converted a poor prognosis form of ALL to a more favourable prognostic group, and combinations of novel therapy such as the D-ALBA approach have provided markedly improved early survival data in adults. The addition of novel therapies to low-intensity chemotherapy approaches such as the MD Anderson Mini-hyperCVD Inotuzumab approach has improved survival in older adults with ALL. Locally the ALL08 study has shown addition of novel therapies has allowed low treatment related mortality in older adults while retaining the ability to attain deep remissions, while the ALL09 study explores the addition of blinatumomab to younger adults with ALL. This talk will discuss how new approaches are helping us meet the challenge of adult and elderly ALL.

3. HSANZ Invited Speakers

Molecular genetics and its impact in AML

Prof Konstanze Döhner
Konstanze Döhner, Department of Internal Medicine III, University Hospital of Ulm, Ulm Germany

In recent years, a number of important cellular pathways have been identified in AML that are now being targeted by novel agents. The development of precision medicine for AML is currently best highlighted by the successful development of first- and next-generation FLT3-inhibitors, such as midostaurin and gilteritinib, the BCL-2 inhibitor venetoclax, and the first-in-class IDH1- and IDH2-inhibitors ivosidenib and enasidenib. Other agents that have entered clinical practice include CC-486, the oral formulation of azacitidine, the hedgehog pathway inhibitor glasdegib, or CPX-351, the liposomal formulation of daunorubicin and cytarabine.
In this session, the impact of molecular markers in AML will be discussed, in particular within the context of risk-stratification/prognostication as well as their predictive relevance. In addition, a brief up-date on ongoing clinical studies with novel agents will be presented, that might alter the standard of care for AML patients in the near future. Finally, relevant aspects on molecular monitoring of measurable residual disease (MRD) as well as clonal evolution will be exemplarily addressed.

Understanding resistance to novel therapies in AML

Assoc Prof Daniel Pollyea
Daniel A. Pollyea, MD

Recently, multiple new and exciting therapies have emerged for patients with acute myeloid leukemia. These therapies have different toxicity and efficacy profiles that have been crucial to understand. In addition, these therapies, many of which have novel mechanisms of action, also have resistance mechanisms that are emerging with more experience. These resistance mechanisms, and ways to predict responses to novel therapies in AML, will be discussed.

A practical approach to CAR-T: Myeloma

Professor Simon Harrison

MM is susceptible to immune control, as shown by a small cure fraction following allo BMT, and the introduction of antibodies such as Daratumab and Elotuzumab. Cell Based therapies chimeric antigen receptor (Car) T cells are effective in B cell malignancies and are now a standard of care therapy in Australia for the treatment of relapsed or refractory ALL and DLBCL targeting the CD19 antigen. There is emerging data to support the use of Car T cells for the treatment of Myeloma and the FDA have recently approved the anti BCMA Car T product idecabtagene vicleucel (ABECMA) in the forth line setting. I will discuss the current evidence to support the use of Car T cell therapies in Myeloma and stragtegies to reduce the risk of the specific Car T related toxicities, cytokine release syndrome, early and late neurotoxicity when treating myeloma patients with this technology.

Relapsed CLL

Dr Mary Ann Anderson
Mary Ann Anderson Haematologist MBBS, FRACP, FRCPA, PhD. The Royal Melbourne Hospital, The Peter MacCallum Cancer Centre, The Walter and Eliza Hall Institute

Treatment options in CLL have expanded exponentially over the last decade with the advent of new classes of drugs primarily the Burton Tyrosine Kinase Inhibitors (BTKi) and the BCL2 inhibitors. Additionally other agents such as PI3 kinase inhibitors and the emerging cellular therapy of chimeric antigen receptor T cells (CART) are also now part of the therapeutic landscape. Combined with superior chemoimmunotherapy regimens these new and emerging treatment modalities have greatly improved the outlook for CLL patients especially those who harbour high risk genetic features or those in whom the disease is relapsed or refractory.

Despite these significant advances, sequencing of these novel therapies with traditional and emerging modalities is not clear and depends on multiple patient and disease characteristics for instance comorbidities which have relevance to toxicity from new agents and genetic risk factors that may influence responses in the short and long term to various therapeutic options. The landscape is further complicated by the absence of head to head clinical trial data to guide decisions in many cases.

In this presentation I will outline a practical approach for clinicians trying to navigate the myriad of clinical trial data to map out a long-term treatment pathway for patients that optimise the balance between toxicity and disease control.

Defining high risk DLBCL

Dr Gareth Gregory

In this presentation Dr Gregory will provide an overview of clinical and biological features portending poor risk to patients with DLBCL. He will discuss how identification of these features may assist to tailor treatment including standards of care according to evidence from past clinical trials and how integration of molecular diagnostics to routine clinical practice may advance the field.

Management of relapsed/refractory aggressive B cell lymphoma

Assoc Prof Tara Cochrane
A/Prof Tara Cochrane: Gold Coast University Hospital

Relapsed and refractory aggressive B cell lymphoma which encompasses both diffuse large B cell and high-grade B cell lymphoma is a challenging clinical entity. To date, management is centred around an autologous stem cell transplant (ASCT), however, this therapy is only appropriate for the younger, fit patient who has a meaningful clinical and radiological response to second line chemotherapy. Moreover, despite ASCT, many patients still succumb from lymphoma relapse. This presentation will discuss ASCT in the current era, where all patients have received rituximab as part of front-line chemotherapy. Potential improvements on salvage therapy will be outlined. The clinical indications, evidence and predictors of response to chimeric antigen receptor T cells (CAR-T), will be outlined. Newer immunotherapy approaches, such as bispecific antibodies, have been developed, and their use in relapsed / refractory aggressive B cell lymphoma is showing considerable clinical promise in early phase studies, even in patients relapsing after CAR-T cell therapy. The role and indications for allogeneic transplant are declining in this space, due to the advent of newer therapies.

Just another Tyrosine Kinase Inhibitor? Updates in Chronic Myeloid Leukaemia

Prof Tim Hughes

For the 300+ patients diagnosed with chronic myeloid leukaemia (CML) each year in Australia there are several excellent tyrosine kinase inhibitors (TKIs) available. Even so, 5-10% will develop advanced phase disease and a similar number will be resistant, or develop resistance to one or more TKI over time. These progressing and resistant patients are responsible for CML-related mortality remaining around 10%. Higher CML-related mortality is seen in low-middle income countries. For the 6,000+ patients in Australia who have achieved a good response to TKI therapy, most remain dependent on ongoing TKI therapy to maintain their remission. There is an urgent need to identify the determinants of poor response, to develop better, safer TKIs, and to understand the barriers preventing most CML patients from achieving treatment-free remission (TFR). The remarkable variability in response to TKI therapy despite all patients sharing the same BCR-ABL target can now be better explained with the availability of longitudinal data on a large cohort of CML patients who have had genomic studies conducted prior to commencing TKI therapy. Genomic variants in addition to BCR-ABL are likely to be the main cause of poor response to imatinib. It is now important to determine which of these “poor risk” genomic variants can be treated more effectively with a second or third generation TKI, and which ones will need a more aggressive or multi-targeted approach to achieve good response. While TKIs are the key determinants of response and outcomes for CML patients, the critical role played by the immune system in mediating initial response, achieving a deep molecular response, and for the lucky few, achieving TFR is becoming increasingly clear. This understanding provides opportunities for new therapeutic approaches which warrant testing in the clinic.

Relapsed and resistant multiple myeloma in 2021 – what should we be doing?

Joseph Mikhael
Joseph Mikhael, MD, MEd, FRCP, Professor, Translational Genomics Research Institute, City of Hope Cancer Center

Multiple Myeloma has undergone a genuine revolution in the last decade – a series of novel agents has resulted in a doubling of overall survival. Indeed, most patients can be expected to live nearly a decade. However, it remains an incredible heterogenous disease with some patients succumbing to the disease even within one year. The complex genetic portfolio of myeloma, along with its intricate interaction with the bone marrow microenvironment accounts for much of this heterogeneity. It also provides multiple potential therapeutic targets to further improve outcomes in myeloma.

The treatment landscape is continually changing and there is no simple algorithm to therapy selection. A few key principles guide our ever-increasing choices for patients. The principles include:

- *Early line therapy influences long term survival* – as remissions tend to shorten over time, it is imperative to use our most effective therapies early on.
    1. *Leveraging multiple mechanisms of action is critical* – when possible class switching is preferred, especially after maintenance therapy.
    2. *When possible, triplet combinations are preferred over doublets* – this has been demonstrated repeatedly in phase 3 trials
    3. *Individual patient selection is based on therapy, disease and patient related factors*. These three categories will guide choice of optimal therapies for enhanced efficacy and minimal toxicity.
    4. *Patient preference should heavily influence selection* – patient engagement and empowerment are critical aspects of treatment choice.

In addition to these principles, an overview of options available in early and late relapse will be discussed. Most patients will eventually develop triple class refractory myeloma, which carries a poor prognosis. However, several novel approaches are now available in this space, including selinexor, belantamab mafodotin, melphalan flufenamide and CAR T cell therapy. A preview of further novel approaches will be briefly presented.

Personalizing treatment for myeloma – are we there yet?

Dr Anna Kalff

Over the last 2 decades, there have been significant improvements in survival for patients with MM, however the clinical course is very heterogeneous due to underlying molecular variations. Treatment of patients with MM is becoming increasingly complex, with triplet therapy now available for newly diagnosed MM and an increasing number of therapeutic options for second-line and beyond, including the recent addition of anti-CD38 monoclonal antibodies to reimbursed treatments on the Australian PBS. Furthermore, there have been significant advances in and more widespread availability of new technologies including molecular profiling (eg: NGS, GEP) to identify predictive/prognostic biomarkers and flow cytometric (and molecular) techniques to assess minimal residual disease (MRD). This presentation with look at understanding the impact of these factors and how we can currently best select therapy (both at diagnosis and subsequent lines) for our MM patients incorporating biomarkers (ie: molecular, genetics) and according to MRD status, as well as future directions.

4. ANZSBT Invited Speakers

Emergency and disaster planning

Dr Heidi-Ann Doughty

Transfusion support is an essential element of modern healthcare and therefore should be considered in emergency and disaster planning. In addition, many national civil contingency arrangements require healthcare providers to prove that they can deal with emergencies while ensuring other critical services. Transfusion communities refer to these arrangements as ‘blood supply contingency’, ‘emergency’ or ‘disaster preparedness’. Preparedness is a dynamic, collaborative process that actively identifies and manages potential and emerging threats. Terrorist events during the 2000s, together with changing trauma and transfusion practice, stimulated a renewed interest in transfusion emergency preparedness. In addition, disasters such as extreme weather, denial and disruption of computer services, and global pandemics continue to challenge transfusion services. Planning and preparation are essential to protect patients and support staff. In this presentation, we consider some of the transfusion principles and practical steps available to prepare for emergencies including business continuity, supporting the hospital transfusion teams, and working in partnership.

National Blood Supply Contingency Plan (NBSCP): Lessons learnt from the COVID-19 pandemic

Sandra Cochrane

Case-study:
The NBA continues to closely monitor blood and blood product inventories.

In 2019, the NBA reviewed the NBSCP, involving extensive supplier and stakeholder consultation. This review found that the NBSCP is a well-established contingency plan within the Australian blood sector, and would benefit from both a structured testing and exercise program, as well as harnessing opportunities to integrate with other contingency planning arrangements in both jurisdictional and Commonwealth environments. During 2020, the NBA worked with a consultant and working group, including representatives from all Commonwealth, State and Territory jurisdictions, to further develop recommendations for a testing and simulation program. Further implementation has been interrupted due to the need for relevant key stakeholders to prioritise pandemic management.

As with many things related to the COVID-19 pandemic, the management of the national blood arrangements during this time has been something of a roller-coaster. As the pandemic evolved during 2020, the demand for fresh blood products was down and supply was up. This situation has been reversed in 2021. Australia's experience is not unlike that of some other countries.

The pandemic has challenged national blood supplies due to stay at home orders, changes to people's movements and lifestyles, and general social anxiety. This has led to many blood donors cancelling their regular donations, or simply failing to attend.

To complicate this, demand for fresh blood is the highest in about ten years. Drivers include the intermittent resumption of previously delayed elective surgery, and increases in emergency presentations in many hospitals across jurisdictions.

This trend is also being seen overseas, with some countries postponing elective surgery to manage blood shortages. While Australia is not yet in this position and we are still above the activation levels of the NBSCP, Lifeblood needs existing donors to increase the frequency of their donations and new donors to come forward.

Conclusion:
The NBA and its stakeholders are pursuing a number of strategies to manage these challenges.

Maintaining Australia's supply of blood during "unprecedented" times

Dr Joanne Pink
Dr Joanne Pink Chief Medical Officer, Australian Red Cross Lifeblood

Australian Red Cross Lifeblood delivers one of the safest blood supplies in the world, as well as world class research and expertise in diagnostic, clinical, transplantation and immunogenetics services. The impact of COVID-19 has been unprecedented and far reaching for all businesses, including the blood and broader health sector.
From the blood sector perspective challenges which will be covered in the presentation include the following:

- Understanding the implications of SARS-CoV-2 and COVID vaccines on blood product safety
    - Introduction of new measures to keep our donor centres places of wellness
    - Understanding and responding to changes in donor behaviours and needs
    - Understanding and coping with fluctuating demands for blood components
    - Management of consumable supply chain disruptions and interruptions to transport routes
    - Introduction of measures to keep our staff healthy, including the rapid transition of office based staff to working from home as well as supporting the mental health of our broader workforce.
    - The collection of convalescent plasma, and related testing programs.
    - Other business continuity challenges, such as the need to quickly move to on-line training

Translational importance of human blood group antigen systems

Dr Christine Cserti-Gazdewich
Dr Christine Cserti-Gazdewich, Transfusion Medicine & Clinical Hematology, University Health Network & University of Toronto, Canada

The sum of red blood cells (RBC) in “the erythron” constitutes the largest organ of the human body. Though devoid of nuclei, mitochondria, or HLA expression at maturity, RBCs are a mechanically resilient and enduring cell type, singularly endowed with the task of gas exchange in the non-gaseous interior of aerobic multicellular organisms. Despite an apparently monotonous mission, this has been a popular and co-evolving target for parasites. On their surface, RBCs distinctively or differentially express a variety of molecular structures, which in turn feature points of variation. These blood group antigen systems are a culmination of evolutionary events, effecting functions, and commanding attention in the everyday service of blood bank compatibility assurance testing. In the structurally imposing “major” systems of ABO and Weiner, ABO links Kingdoms and shapes the outcomes of infections as ancient as malaria or as new as COVID-19, while the Weiner system exerts a seemingly fractal diversity and matching challenge for the very founders of all founder subgroups. “Minor” systems with more overt functional significance count an increasing number of altered members with immunogenic facades and elicited antibodies. Among the most interesting is the Atypical Chemokine Receptor 1 (ACKR1), also known as the Duffy Antigen Receptor for Chemokines (DARC). The relationship between genotypes and phenotypes may be more complicated than the mere presence or absence of something, with a range of weak (non-antigenic), partial (antigenic), or unknown significance effects for an affected individual or a blood donor-recipient pair. The underestimation of erythroid portals, pegs, and evolutionary timepieces ends in the face of the science that followed the seemingly once simple enterprise of blood matching.

Military transfusion and its influence on civilian transfusion practice

Dr Heidi-Ann Doughty

Critical bleeding is the most immediate threat to the severely injured. The mortality rate after massive haemorrhage in trauma is high unless actively managed from the point of injury with haemorrhage control and resuscitation. The recent conflicts in Iraq and Afghanistan stimulated considerable innovations in trauma healthcare including transfusion. Blood based resuscitation emerged as an essential and successful element of early combat care. The paradigm of military transfusion practice changed rapidly, and the developments were credited with contributing to the survival of the critically injured. The changes in practice were underpinned by a revised understanding of trauma patho-physiology and took place during a period of significant regulatory change. Many of the recent lessons from military healthcare have already influenced civilian practice including the re-organisation of trauma services and changes in clinical practice. Transfusion specific examples include the management of massive haemorrhage, pre-hospital transfusion and the transfusion planning for major incidents. These have been enhanced through the emphasis on team training and non-technical skills. Success has been due to global, multi-disciplinary partnership and has the potential to benefit the wider healthcare community.

Platelet and neutrophil antigen testing: What's new?

Mark Burton

Platelet and neutrophil antigen testing: What's new?
Human platelet (HPA) and human neutrophil antigen (HNA) testing is essential for laboratories performing investigations of immune thrombocytopenia and neutropenia.
Across the world a variety of in-house and commercial typing methods are utilised with the focus predominately identifying the single nucleotide polymorphisms responsible for the most common and clinically relevant HPA and HNA.
Compared to these common methods, next generation sequencing (NGS) typing provides higher resolution with the opportunity to identify rarer alleles while cell free DNA (cfDNA) provides less invasive foetal typing. Integrating these more complex NGS and cfDNA techniques into a testing algorithm requires decisions based on striking a balance between the more extensive results available and the results required for the clinical situation.

Paediatric haemovigilance/ SHOT

Dr Anne Kelly

Paediatric haemovigilance is a distinct entity, as evidenced by the longstanding paediatric reports and recommendations from the UK national haemovigilance scheme ‘SHOT’. The lessons learned from repeated errors have provided the basis for specialist education and revised national guidelines. This work compliments studies in children, including those looking at mechanisms underlying adverse events and trials of clinical outcomes following transfusion. Work to improve the definitions for adverse events following paediatric transfusion will improve future understanding of the true incidence of significant adverse outcomes, and will more fully inform clinical decisions on the risk/benefit for individual patients

What's on the horizon for haemovigilance in Australia?

Alison Street

The National Blood Authority's (NBA) Haemovigilance Advisory Committee (HAC) provides advice to the NBA on the development and implementation of the Strategic Framework for the National Haemovigilance Program. This framework defines the scope of activities that contribute to national standardisation at the level agreed in the Australian Haemovigilance Minimum Data Set (AHMDS) as endorsed by jurisdictions in 2014. Both the strategic framework and AHDMS are under review and revised versions are due for release in late 2022-3. The AHMDS is being updated to reflect current international definitions.

It is an accreditation requirement for Australian Health Service Organisations (HSO) to participate in haemovigilance activities and report adverse events. The national program relies upon data receipt from HSOs and jurisdictional systems to whom HSOs report. With voluntary inputs currently being received from multiple state and territory sources, consistent, good quality and timely data suitable for informed national analysis is not assured

The NBA is currently exploring a range of priority areas, including barriers to consistent, quality data and reporting so as to identify opportunities that will improve national haemovigilance performance and reporting within the current health system.

Other initiatives being reviewed and further developed within the National Haemovigilance Program include Educational and Audit Activities

Critical incident investigation

Ms Trish Roberts

Critical incident investigations are often seen as the catalyst for organisational change after a serious adverse transfusion-related event. However, what defines a critical incident? Are they only the events that have resulted in significant morbidity or even death, or are they all deviations from policy that could have resulted in harm? This presentation will challenge the audience's thinking about critical incidents, highlight the importance of near miss events and provide strategies to optimise your organisation's safety culture.

With the aim of encouraging the audience to consider incorporating near miss event investigations to hold the same level of importance as critical incidents. Making transfusion safer occurs when we can learn and understand the array of causative factors that contributed to both critical incidents and near misses but the challenge often faced by many in the health care sector is how to sustain necessary change needed in the clinical setting with ongoing competing priorities.

Evidence-based transfusion in neonates

A/Prof Amy Keir

Transfusion of blood products remain common in neonatal units around the world. Preterm infants are the most heavily transfused patient population with the longest life span. Despite this, the use of blood products outside of evidence-based clinical guidelines and significant variation in practice continues to occur. These practices persist despite improvements in the evidence base for transfusion, the existence of clinical guidelines, and numerous initiatives, including patient blood management, to reduce the inappropriate use of blood products.

It remains a complex endeavour to change clinicians' practice to align with best practice by getting them to stop using various interventions that are not supported by evidence, free from harm and truly necessary. My talk focuses on using quality improvement to bridge the gap between evidence-based knowledge and neonatal transfusion practice.

To transfuse or not to transfuse?

Dr Catherine Cole

While there are many publications supporting restrictive transfusion practices in children in critical care, little is written about transfusion where alternative treatments are available and where guidelines do not support transfusion.
This presentation will discuss transfusions in children with sickle cell disease and those with iron deficiency.

Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT)

Prof Toby Richards
Richards, Toby et al. The Lancet, Volume 396, Issue 10259, 1353 – 1361
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31539-7/fulltext

Methods: PREVENTT was double-blind, parallel-group randomised trial, patients with anaemia 10-42 days before elective major open abdominal surgery were randomised to receive intravenous iron or placebo 10–42 days before surgery.

Findings: Of 487 participants randomly assigned to placebo (n=243) or intravenous iron (n=244) between Jan 6, 2014, and Sept 28, 2018, complete data for the primary endpoints were available for 474 (97%) individuals. Death or blood transfusion occurred in 67 (28%) of the 237 patients in the placebo group and 69 (29%) of the 237 patients in the intravenous iron group (risk ratio 1·03, 95% CI 0·78–1·37; p=0·84). There were 111 blood transfusions in the placebo group and 105 in the intravenous iron group (rate ratio 0·98, 95% CI 0·68–1·43; p=0·93). There were no significant differences between the two groups for any of the prespecified safety endpoints.

Interpretation: Preoperative intravenous iron was not superior to placebo to reduce need for blood transfusion when administered to patients with anaemia 10–42 days before elective major abdominal surgery.

Funding: UK National Institute of Health Research Health Technology

Electronic management of PBM data (REDcap)

Kylie Symons
Kylie Symons, Clinical Nurse Consultant Patient Blood Management

Pre-operative screening and treatment of iron deficiency and anaemia is proven to reduce infectious and thrombotic complications, blood transfusion, mortality and hospital length of stay whilst contributing to significant improvements in overall hospital net costs. This presentation will discuss the implementation of a REDCap (Research Electronic Data Capture) tool to support Patient Blood Management (PBM) programme delivery at Fiona Stanley Hospital, the major tertiary hospital in the south metropolitan area in Western Australia. The integration of REDCap directly into Western Australia Department of Health information systems has allowed for rapid and safe diagnosis, management, and timely optimisation of the patient prior to surgery through inbuilt decision assist algorithms. REDCap provides safe and secure patient data capture, reduces clinical ICT workload, and permits rapid audits to drive contiuous positive change.

Transfusion support for patients with haematological malignancies

Dr Christine Cserti-Gazdewich
Dr Christine Cserti-Gazdewich, *Transfusion Medicine & Clinical Hematology, University Health Network & University of Toronto, Canada*

Patients with haematological malignancies (HM) often require, and thus drive a significant proportion of, the utilization of red blood cells [RBC], platelets [PLT], and immune globulins [IG]. However, the “wisest” quantitative and qualitative parameters-of-use for each of these goods are not always clear in HM, particularly in relation to the nuances and goals of inpatient versus ambulatory care. Should hematocrits run higher with age, or with the prioritization of quality-of-life, or for hemostasis during severe thrombocytopenia? If evidence on conservative triggering from inpatients is not generalizable to outpatients, what should the more liberal limits on RBC and PLT use be? When can (or should) blood products be used to enable access to certain interventions? How are evolving treatments in HM shifting the anticipated demand for IG when global supplies are increasingly strained? How do risks of transfusion compare in HM, and how do the vulnerabilities in this population influence mitigation and personalization strategies, from patient premedication practices to additional product attributes (eg irradiation, plasma/[supernatant] volume reduction [± additive solution replacement], pathogen inactivation, and varying depths of antigen matching)? Appreciating the many dimensions of transfusion care in HM is key to providing the best range of products needed at an individual and dynamic program level.

Blood prescribing in EMR: Is it best practice?

Dr Philip Crispin

Medical records have been evolving into electronic forms over many years, often with individual systems in different departments. Ease of access, reducing the mountains of paper and decision support will drive further expansion. Potential advantages for blood transfusion include more appropriate transfusion driven by decision support, improved efficiency and safer patient identification. These benefits cannot be assumed. Clinical pathways already guide safe practice. Failure to attend to safe clinical workflows in conjunction with EMRs may increase risks, while engagement by vendors and institutions with the clinical workforce can liberate added value from EMRs. Guidelines enable institutions and vendors to build EMRs to common goals and requirements.

5. THANZ Invited Speakers

Platelet gene expression in myeloid malignancies

Dr Belinda Guo
Belinda B Guo School of Biomedical Sciences, University of Western Australia, Crawley, W.A., Australia

Abstract
Platelets are increasingly being explored as a clinically useful cancer biomarker and have been reported to have distinct mRNA profiles associated with solid tumours (e.g. breast, pancreatic, lung cancers). We have used a whole transcriptomic approach to study gene expression in platelets in myeloid malignancies. In myeloproliferative neoplasms, platelet gene expression differs from normal and this is most marked in those with increased reticulin. We identified >1,000 genes that were uniquely differentially expressed with the most significant involved in DNA repair regulation, replication and cell cycle progression. A putative 3-gene platelet fibrosis-associated signature (*CCND1*, *H2AX* and *CEP55*) could discriminate between patients with and without fibrosis with 88% accuracy. Platelet gene expression abnormalities may be due to derivation from clonally-defective megakaryocytes in myeloproliferative neoplasms. These findings suggest platelets may have clinical utility in detecting genomic alterations that arise during the natural history of the disease.

How to treat immune thrombocytopenia (ITP) that has not responded to first line treatment

Dr Robert Bird

An important consideration when patients with a provisional diagnosis of ITP fail initial treatment is an alternative diagnosis.
Until recently, first line treatment of newly diagnosed ITP employed steroids +/- ivIg. Despite efforts over the years to optimise choice of steroid and scheduling, little improvement in efficacy had been gained. The recently published FLIGHT study (Bradbury, C et al NEJM Sept 2021) has demonstrated that the addition of mycophenolate to first line treatment could substantially increase initial response rates and decrease subsequent relapse rate, becoming the new first line standard of care.
Restrictions on accessing subsidised thrombopoietin receptor agonists means that splenectomy remains the definitive treatment for relapsed/refractory ITP, but a common theme in ITP management guidelines is that this surgery should be defer until ITP progresses to chronic phase. Therefore, treatments which can bridge to, or preferably avoid splenectomy are needed. It is important to remember that splenectomy is almost never an inclusion criterion in clinical trials, so referral to your local ITP trials centre is likely to serve the dual purpose of review by a haematologist with a larger ITP caseload and access to a clinical trial, if available.

Management of incidental/subsegmental pulmonary embolism

Prof Christopher Ward
Prof C Ward, Dept of Haematology, Royal North Shore Hospital, St Leonards NSW; University of Sydney

With widespread use of high-resolution CT scans for diagnosis and monitoring of many disorders, the finding of small-volume and isolated pulmonary emboli (PE) has become a clinical quandary. Many of these patients have no or minimal symptoms related to the clot, and the optimal management of these cases is unclear. Expert review of imaging to rule out artefact may be needed, including a formal CTPA. Incidental PE is most commonly seen in cancer patients; cohort studies have shown that these "asymptomatic" events are associated with poor outcomes, including recurrent VTE and reduced overall survival. Hence, most clinicians will treat incidental PE in cancer with full anticoagulation, similar to the management of symptomatic PE. There is less clarity on the management of subsegmental/incidental PE in lower-risk patients; expert groups have proposed a strategy of observation alone (after ruling out lower limb thrombi) but there is a lack of evidence to support this approach. A prospective study of observation for incidental PE in patients without cancer or prior VTE has just been reported. The study found a higher than expected incidence of recurrent VTE (1.1% per month) and was ceased before full recruitment. Patients aged under 65 and with a single subsegmental PE had lower risk of recurrence , suggesting that observation rather than anticoagulation can be justified in selected patients with incidental PE

Distal deep vein thrombosis

Eileen Merriman
Clinical Director of Haematology and Lead Thrombosis Clinician at North Shore Hospital, Auckland, New Zealand.

Distal DVT comprise 50% of all DVT diagnosed by ultrasound. The management is controversial, ranging from no anticoagulation and repeat ultrasound at 7-10 days, through to three months full dose anticoagulation. The epidemiology, presentation, diagnosis and management of distal DVT will be discussed, with reference to recent trials in this area.

6. Nurses Invited Speakers

The Care Plus implementation study: Integrating early palliative care for people with blood cancers

Prof Jennifer Philip

Despite a mature body of evidence supporting early integration of palliative care for people with cancer, translation into practice remains, at best, variable. Barriers including perceptions of palliative care held by patients and clinicians, uncertainty about optimal timing and referral processes, as well as interdisciplinary relationships all contribute. To advance the field, robust implementation processes are required. Care Plus is an integrated model of palliative care introduced at standardised illness points as a practice change for patients with cancer including blood cancers.
Aim: We are seeking to implement Care Plus for patients with blood cancers reaching key points in their illness across three hospitals.
Methods: Based on implementation science principles, a series of steps of engagement, planning and delivery were developed in collaboration with the treating haematology teams. Using the RE-AIM implementation framework, we are evaluating the processes of implementation collecting qualitative and quantitative of Reach, Effectiveness, Adoption, Implementation & Maintenance. Further we are measuring the outcome of the practice change using population level health service use data pre/post implementation.
This presentation will discuss the implementation findings and the preliminary effectiveness outcomes of this ongoing study.
Implications: Our preliminary data suggest the Care Plus delivery model is feasible and acceptable for people with blood cancers, with standardised patient identification and clinician relationships enhanced by the implementation of this care pathway.

Quality of life following Allogeneic Stem Cell Transplantation at Alfred Health

Ms Bianca Cirone

Aim
To assess quality of life (QOL) following allogeneic stem cell transplantation (SCT) and determine what impact chronic graft-versus-host disease (cGvHD) has on QOL measures.

Method
Individuals who attended the late effects clinic two years and beyond SCT who were disease free from a blood cancer or its treatment completed the Functional Assessment of Cancer Therapy – Bone Marrow Transplantation (FACT-BMT) Scale. Study questionnaires were conducted and returned via hard copy following obtainment of consent. Results were analysed from a comprehensive database. The presence of cGvHD, previous or active was obtained from the SCT database.

Results
Questionnaires were analysed on 151 consecutive participants from June 2017 - June 2019. The majority of participants had a diagnosis of acute leukaemia (53%) and were on average 2.5 years post transplant with a range of 2 to 20.9 years. cGvHD was documented in 47% of participantsTable 1 shows the comparison of QOL domain scores between the cGvHD and non-GvHD cohort using norm-based T scores. T-scores are standardised scores with 50 representing the mean; a mean of 50 represents the mean score of the general population [1].

Table 1:

	Female participant %	Physical domain	Social domain	Emotional domain	Functional domain
Non-GvHD participant cohort	46%	47.9	55.7	48.1	52.5
cGvHD participant cohort	45%	40.2	53.1	44.1	48.9

Conclusion
Participants in the non-GvHD cohort appear to have generally favourable perceptions of their QOL post SCT. The cGvHD cohort scored significantly lower in all four domains. Both groups report poorer QOL in the physical and emotional domains. Despite this, both groups report higher QOL in the social domain relative to the norms, indicating strong support as a facilitating factor of better QOL and enhanced interpersonal relationships and thus some degree of enhanced life satisfaction. Future efforts will be directed at attempts to meet patients' educational needs and expectations at the SCT preparatory phase, particularly in relation to cGVHD and to explore outpatient services for patients living with prevalent symptoms following SCT.

References:
1. Psycho-oncology Co-operative Research Group. PoCoG – Psycho-oncology Outcomes Database Normative Data Calculator. Queensland Cancer Risk Study, 2014. www.pocog.org.au

CAR T cell

Maddie Gilsenan

Chimeric Antigen Receptor T-cell (CAR-T) therapy has revolutionised the treatment of relapsed/refractory B- cell acute lymphoblastic leukaemia (ALL) in adult and paediatric patients where standard therapies have failed. CAR-T therapy is comprised of a complex treatment pathway, from referral through to post infusion care, requiring involvement from many specialities within the multidisciplinary team.
A reflection on the collective efforts and lessons learnt from the first paediatric CAR-T referral centre in Australia and New Zealand will be provided, highlighting the specialised nursing care required to deliver this therapy.
An overview of the unique toxicities commonly associated with CAR-T therapy, specifically Cytokine Release Syndrome (CRS) and Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS), will be provided to assist nursing staff with their recognition and management.

Understanding the ITP rollercoaster - a patient's perspective

Danielle Boyle

Danielle has had Immune Thrombocytopenia for more than 6 years. She's experienced many highs and lows throughout the past 6 years and will be providing first hand experience and insights into how many ITP Patients experience this life long rare disease, and how ITP Australia came about and how she's now providing support for other ITP patients and carers.

The power of storytelling in illness

Dr Barry Quinn
Dr Barry Quinn RN, Queen's University Belfast

Human beings are both gifted and burdened by the ability to reflect on the meaning of life
This presentation explores the presence and the beauty of personal storytelling in the context of living with illness. The presentation, begins with the premise that a central component of being human is the ability to engage with creating our own personal story and making sense of that reality. Using insights from my own practice and research, and the personal stories of people living with cancer, I will explore this important aspect of care. Paying attention to stories and this sense making activity, may help in directing the focus away from the idea of 'the patient' and providing a useful account of what might be demanded if we take the idea of 'person centred care' seriously. Having explored the search for meaning in illness and having illuminated the sometimes overlooked personal story behind cancer, the presentation offers practical insights into better understanding and responding to the personal story of illness.

7. BMTSAA Invited Speakers

Cryopreserved HPC graft quality during COVID

Dr Duncan Purtill

Changes to donor availability, collection centre capacity and travel restrictions during the early phase of the COVID-19 pandemic led to routine cryopreservation of most unrelated donor products for haematopoietic transplantation prior to the recipient commencing the conditioning regimen. In collaboration with the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), laboratories and transplant centres across the region investigated factors that influence the quality of cryopreserved haemopoietic progenitor cells (HPC) and the outcome of unrelated donor product procurement and transplantation during the first six months of the COVID-19 pandemic.
Analysis of 305 products cryopreserved prior to the pandemic revealed significant variation in post-thaw CD34 recovery and viability, with an association between poor post-thaw quality and longer liquid storage time, higher white cell count and complex pre-cryopreservation manipulation.
A subsequent analysis of 191 products collected between 01 April 2021 and 30 September 2021 revealed satisfactory CD34 recovery and viability. Furthermore, time to neutrophil and platelet recovery were similar to that observed from 'fresh' unrelated donor HPC transplantation prior to the pandemic. However, a significant proportion (29%) of cryopreserved unrelated donor products did not comply with documentation, labelling, packaging or dose requests from the transplant centre, and receiving transplant laboratories reported increased workload co-ordinating cryopreserved donor logistics. Furthermore, 14% of unrelated donor products had not been infused at the time of data collection.
Routine cryopreservation of unrelated donor HPC products has enabled safe continuation of allogeneic transplant services during the COVID-19 pandemic. However, practices for product tracing, documentation and transportation can be optimised, and measures to reduce the incidence of unused unrelated donor product are required.

8. Presidential Symposia

08.01

Novel procoagulant platelet assay for diagnosis of Vaccine Induced Thrombocytopenia and Thrombosis

Dr Vivien CHEN[1,4],
Dr Christine Lee[1,4], Dr Timothy Brighton[2], Dr Freda Passam[3,4], Dr Emmanuel Favaloro[5]
[1]Concord Hospital, ANZAC Research Institute, Concord, Australia, [2]SEALS Pathology, Randwick, Australia, [3]Royal Prince Alfred Hospital, Camperdown, Australia, [4]University of Sydney, Sydney, Australia, [5]ICPMR, Westmead, Australia

Background: VITT is a serious complication of ChAdOx1-nCov-19 vaccination in which antibodies against PF4/polyanion complexes are thought to activate platelets via platelet FcgammaRIIa. Detection of platelet activating antibodies are requisite for confirming the diagnosis of VITT. Early recognition is key to improved outcomes.

Aim: To evaluate a procoagulant platelet assay designed to detect antibody mediated platelet signalling in VITT diagnosis.

Method: Australian patients referred for confirmatory VITT testing with probable or possible VITT (confirmed thrombosis with symptom onset within 4-30 days after ChAdOx1-nCov-19 vaccination with D-Dimer > 5x ULN, platelets < 150 x 10^9/L or falling platelet count) were screened using a PF4/polyanion ELISA. Our previously established flow cytometry-based procoagulant platelet assay was modified to incorporate exogenous plasma, performed using platelets from healthy donors screened for FcgammaRIIa responsiveness after stimulation with 5uM SFLLRN. A positive result was defined as a >2 fold increase of procoagulant platelets in presence of patient plasma that suppressed in presence of 100U/mL heparin or monoclonal FcgammaRIIa blocking antibody, IV.3. ELISA positive patients and flow cytometry positive patient also tested by serotonin release assay, multiplate aggregometry. Clinical correlation was obtained.

Results: 60 unique patient samples were tested from citrated plasma of patients with suspected VITT. In presence of plasma from patient with thrombocytopenia unrelated to FcgammaRIIa stimulating antibodies (including sepsis and consumptive coagulopathy), procoagulant platelet formation was minimal after stimulation with SFLLRN. 26 samples were PF4/polyanion ELISA positive. 24 of 26 ELISA positive samples induced demonstrated a pathological procoagulant pattern in the flow cytometry assay. Samples with a classical VITT pattern on flow cytometry with ELISA OD>1.0 also demonstrated heparin independent platelet activation on SRA testing. 5 patients with positive ELISA with OD<0.99 were positive by flow cytometry but negative on SRA testing.

Conclusion: A procoagulant flow cytometry assay successfully detected VITT with high sensitivity

08.02

Snakebite associated thrombotic microangiopathy in the Australian Snakebite Project

Associate Professor Tina Noutsos[1,2,3],
Professor Bart J Currie[1,2], Dr Katherine Z Isoardi[5,6], Professor Simon G Brown[4,7], Professor Geoffrey K Isbister[6]
[1]Royal Darwin Hospital, Darwin, Australia, [2]Menzies School of Health Research, Darwin, Australia, [3]Flinders University, Darwin, 0810, [4]Ambulance Tasmania, Hobart, Australia, [5]Princess Alexandra Hospital, Brisbane, Australia, [6]University of Newcastle, Newcastle, Australia, [7]University of Western Australia, Perth, Australia

Aim: Snakebite-associated thrombotic microangiopathy (TMA) occurs in a subset of patients with venom-induced consumption coagulopathy (VICC) following snakebite. Acute kidney injury (AKI) is the commonest end-organ manifestation of TMA. The epidemiology, diagnostic features, outcomes, and effectiveness of interventions including therapeutic plasma-exchange (TPE), in snakebite-associated TMA are poorly understood.

Method: We reviewed all patients with suspected or confirmed snakebite recruited to the Australian Snakebite Project (2004-2018 inclusive), a prospective cohort study, from 202 participating Australian hospitals across the country. TMA was defined as anaemia with schistocytosis.

Results: 2069 patients with suspected snakebite were enrolled, with 1158 (56.0%) systemically envenomed, of which 842 (72.7%) developed VICC, from which 104 (12.4%) developed TMA. Of those systemically envenomed, TMA occurred in 26% (13/50) taipan, 17% (60/351) brown, and 8% (16/197) tiger snakebites. Thrombocytopenia was present in 90% (94/104) of TMA cases, and a further eight (8%) had a >25% decrease in platelets from presentation. Patients with TMA were significantly older than non-TMA patients with VICC (53 [35-61] versus 41 [24-55] years, median [IQR], p<0.0001). AKI developed in 94% (98/104) of TMA patients, with 34% (33/98) requiring dialysis (D-AKI). There were four deaths. In D-AKI TMA cases, eventual dialysis free survival (DFS) was 97% (32/33). TPE was used in five D-AKI cases, with no significant difference in DFS or time to independence from dialysis. >90-day follow up for 25 D-AKI cases (130 person-years) showed no end stage kidney disease but 52% (13/25) had ≥Stage 3 chronic kidney disease (CKD).

Conclusion: Our findings support a definition of snakebite associated TMA as anaemia with schistocytosis and either thrombocytopenia or >25% drop in platelet count. AKI occurring with snakebite-associated TMA varied in severity, with most achieving DFS, but with a risk of long-term CKD in half. We found no evidence of benefit for TPE in D-AKI.
No conflict of interest to disclose.

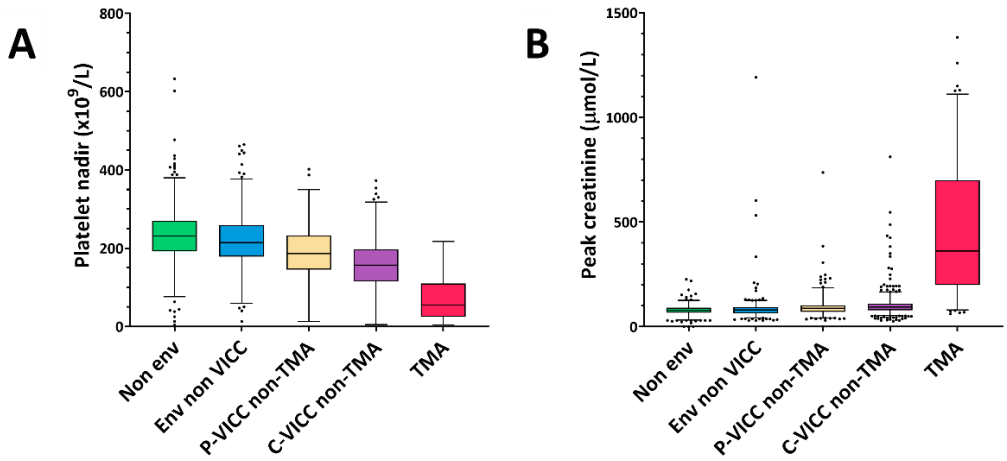


Figure 1: *Platelet nadir (A) and peak creatinine for non-envenomed (non-env), envenomed non VICC, partial VICC (P-VICC), complete VICC (C-VICC) and thrombotic microangiopathy (TMA) cases*.

08.03

Integrated clinical, molecular and genomic evaluation of Guadecitabine (SGI-110) in peripheral T-cell lymphoma (PTCL): the phase 2 STELLAR study

Associate Professor Jake Shortt[1,2,4] Dr Jonathan Wong[1,2], Dr Lev Kats[3,4], Dr Mark Waltham[2], Dr Ian Jong[1,2], Dr Sidney Levy[1,2], Mr Quinton Luong[2], Dr Zahra Sabouri-Thompson[2], Ms Belinda Maher[1,2], Dr Daniella Brasacchio[2], Ms Wendy Jia[3], Dr Joan So[3], Dr Emily Gruber[3], Mr Hugh Skinner[3], Ms Carmen DiCorleto[1], Ms Micheleine Uhe[1], Ms Jeanette Gamgee[1], Professor Stephen Opat[1,2], Dr Gareth Gregory[1,2], Dr John Reynolds[2,5], Dr Eliza Hawkes[2,6,7], Dr Gajan Kailainathan[8], Dr Robin Gasiorowski[8,9],
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Aim: PTCL shares mutations with myelodysplasia (MDS) and azacitidine has activity in both diseases. Guadecitabine, a 'next-generation' hypomethylator, has undergone phase 3 evaluation in MDS. We evaluated the safety and efficacy of guadecitabine in PTCL.

Method: Phase 2 trial of guadecitabine in relapsed/refractory PTCL or unfit treatment-naïve patients (± concurrent MDS). Primary (safety/ORR) and secondary (PFS/OS) endpoints were annotated by total metabolic tumour volume and NGS of cell free DNA (cfDNA). Molecular correlates were further investigated by an epigenetically targeted CRISPR screen.

Results: 20 patients were recruited at two sites with median age 65 [range 51-81], 14/20 male, stage III/IV 100%, ECOG 2/3 30%. Diagnoses: PTCL-TFH [16], PTCL-NOS [2], ALCL [1], EATL [1]. Median prior lines: 3 [range 0-9]; 2 treatment-naïve patients (1 with MDS); 40% post-transplant. Subjects received median 3.5 cycles [range 1-16]. Commonest AEs were febrile neutropenia (60% in cycle 1) and thrombocytopenia (Gr≥3 15%). ORR was 40% [2 CR+6 PR], with a 50% disease control rate [stable disease>6 cycles +CR/PR]. At median 10m follow up, PFS and OS were 2.9m [95% CI: 1.6-7.9m] and 10.3m [95% CI: 2.9-18.3m]. 16 patients discontinued due to progression; 1 underwent allograft following CR and 6 were alive at follow-up. cfDNA demonstrated MDS-associated mutations in 19/20 patients. *TET2*/*DNMT3A* mutations did not correlate with response. Responses occurred in 5/7 patients with mutant *TP53*. *RHOA* mutation predicted improved PFS (5.47 vs 1.35m; p=0.02). CRISPR screening showed that *TET2* loss conveyed guadecitabine resistance. Deletion of histone demethylases and *SETD2* sensitized to guadecitabine. *SETD2* is mutated in EATL and correlated with an objective clinical response (PR and >50% reduction in TMTV).

Conclusion: Guadecitabine conveyed a high disease control rate with acceptable toxicity. *RHOA* mutations correlated with improved PFS. Deletion of histone demethylases and *SETD2* (but not *TET2*) sensitized to guadecitabine. As PFS was suboptimal, hypomethylator combination therapies are needed to improve outcomes.

08.04

First Report on Efficacy and Safety of Commercial CAR-T cell Treatment in Australia

A/Prof Michael Dickinson[1], Dr Adrian Minson[1], Dr Mark Dowling[1], Dr Edward Abadir[4], Dr Jason Butler[5], Dr Seong Lin Khaw[10], Prof Tracey O'Brien[10], Prof P.Joy Ho[4], Dr Chris Fraser[2], Nicole O'Leary[1], Leonie Wilcox[9], Dr Richard Mitchell[10], A/Prof Emily Blyth[8], Dr Duncan Purtill[6], A/Prof Nada Hamad[9,3], Prof Simon Harrison[1], Steven Tran[9],
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Aim: CD19 CAR-T cell therapy for DLBCL and paediatric/adolescent ALL (pALL) was approved by the TGA in Dec 2018 and was funded in 2019. We report the initial experience of commercial CART cell therapy across treating centres, as captured by the ABMTRR

Method: The AMBTRR is a prospective registry that is active at all CART sites. A detailed CART-specific REDCap database was established in collaboration with sites. Detailed fields include demographics, treatment, toxicities, response and survival outcomes. The data cut-off was 5 Feb 2021.

Results: 61pts were included from 3 adult and 2 paediatric sites; 57 were infused, 29 pALL and 28 DLBCL, with a median FU of 170 and 99 days. Any FU and 100 day FU is available in 93% & 38% pALL and 86% & 61% in DLBCL. Median time from manufacturing order to receipt was 24 days. Best ORR was 79% for DLBCL (63% CR, 17% PR), with PFS at 100d of 57%; for pALL the BORR was 93%, and PFS was 93% at 100d. Toxicities are listed in the table.

NR = not reported		pALL (n=29)	DLBCL (n=28)
Characteristics	Median Age	13	65
	Male / Female (%)	52/45 (3% NR)	75/25
	Prior HSCT (%)	39%	50%
	Bridging	76% (17% NR)	79% (3.6%NR)
		pALL (n=18)	DLBCL (n=24)
Toxicity	CRS	61% (17% Gr 3)	88% (0% Gr 3/4)
	Neurotoxicity	11% (1 pt Gr3)	4%
	TLS	4%	Nil (?)
	Hospitalisation	61% (NR in 39%)	79% (NR in 17%)
	ICU	17%	4%
	Toci Use	22%	33%

Conclusion: CART treatment is increasing for DLBCL and approximates anticipated annual numbers in preliminary data suggest CAR-T outcomes are within expectations from published data. We anticipate significantly updated data will be available for presentation in September.

08.05

Establishment of a national clinical haematology education programme – 12 month progress report

Dr Wei Jiang[1,2] *Dr Helen Moore*[3], *Dr Anna Hutchinson*[4], *Dr Maya Latimer*[5], *Dr Matthew Wright*[6], *Dr David Yeung*[8], *Dr Rebecca Adams*[8,10], *Dr Sally Campbell*[9], *Mr Tom Reidy*[12], *Dr Jim Griffiths*[10], *Nada Hamad*[11,13]
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Aim: To implement a national clinical haematology teaching program in response to a need identified by surveying haematology trainees at the 2017 HAA Trainees Day.

Method: A SWOT analysis identified opportunities for developing an interactive online programme by experienced clinicians to supplement evolving evidence-based practice, relevant to a local context. A steering committee of haematologists from Australia and New Zealand developed a curriculum proposal endorsed by the Committee for Joint Training in Haematology (RACP and RCPA) and the HSANZ. Course content was recorded in 2019 and the programme launched in 2020 on MD Briefcase, an online continuing medical education platform. Funding was sourced from industry, independent of program development and clinicians. The program has been provided at no cost to participants, as an approved CPD activity. Ongoing evaluation, reporting of usage patterns and participant feedback has informed quality improvement.

Results: 181 participants enrolled in the programme between March 2020 and March 2021. 55% were haematologists, 30% trainees and 15% other clinicians (pharmacists, nurses). 21 online modules were delivered by haematologists expert in each field, with updates for modules in which evidence-based practice is changing rapidly. 7 modules had between 90-100% participation – Multiple Myeloma, CLL, ALL, Hodgkin Disease, Low/High Grade Non-Hodgkin Lymphoma and T cell Lymphoma. 74-93% of respondents who had completed these modules felt their learning objectives had been entirely met and 100% of respondents felt them relevant to their clinical practice. Objective assessment of knowledge acquisition was assessed using multiple choice questions before and after the module. There was a 25% improvement in the number of correct answers (67% pre-test, 84% post-test) across the modules with highest participation. Opportunities for improvement were identified by faculty and participants, including expanding the curriculum, shorter presentations on specific ‘hot topic’ areas, a more user-friendly interface and a better system for monitoring user metrics.

Conclusion: A national standardised online clinical haematology education programme has been implemented with high engagement. Ongoing continuous quality improvement is underway.

08.06

"Real World" Outcomes for Patients diagnosed with Systemic AL Amyloidosis in Australia

Dr Simon D Gibbs[2],
[1]Fiona Stanley Hospital, Perth, Australia, [2]Eastern Health, Melbourne, Australia

Aim: Data regarding outcomes in systemic AL amyloidosis (AL) patients in Australia is lacking. We sought to audit patients characteristics and outcomes in two amyloidosis services within Australia.

Method: Patients diagnosed with AL between 2017 to 2020 were identified via electronic medical records at Eastern Health (EH) and the Fiona Stanley Hospital (FSH). Patient demographics, treatment and outcomes were collected and analysed.

Results: 79 patients were diagnosed at EH, and 20 at FSH of which 77% had lambda and 23% kappa AL. Five patients had IgM associated AL.

Median age was 65 (range 33-84), and 68% (n=67) were male. 74% had cardiac, 55% renal involvement, with 35% of patients having more than two organs involved. Revised Mayo Staging was: I = 44%, II 25%, III 34%, IV 27%. Renal stage was I, II, and III in 58%, 34% and 8% respectively.

Frontline treatments were: Bortezomib/cyclophosphamide/dexamethasone (VCD) in 75 (76%); VCD and daratumumab in 2 (2%); lenalidomide based in 4 (4%); cyclophosphamide/dexamethasone in 6 (6%) and melphalan based in 4 (4%). Three patients did not receive treatment.

Haematologic response data was available in 94 patients. 29 (31%) achieved a complete response, 23 (24%) a very good partial response, and 28 (30%) a partial response corresponding to an overall response rate of 85%.

Median follow-up was 28 months for the cohort. At last follow up 34 patients have died. Median progression free survival was 18 months and median overall survival was not reached for the cohort. 16% of patients died within six month of diagnosis.

Conclusion: VCD is the most common treatment for AL amyloidosis. Clonal response rates are similar to those seen in Andromeda. Early mortality remains significant particularly for those with cardiac disease. Early institution of daratumumab may improve clonal response rates and patient survival.

08.07

Calcium is a key mediator of the phenotypic changes in cryopreserved platelets

Dr Lauren Waters[1], *Dr Matthew Padula*[2], *A/Prof. Denese Marks*[1,3], *Dr Lacey Johnson*[1]
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Aim: Cryopreserved platelets are phenotypically and functionally different to conventionally stored platelets. Calcium is essential for platelet signalling and activation, and the higher intracellular calcium concentration observed in frozen platelets may also be responsible for cryopreservation-induced alterations. As such, calcium chelation was used as a tool to explore the role of calcium in mediating phenotypical changes in cryopreserved platelets.

Method: Two buffy-coat derived platelets were pooled, split and cryopreserved using 5-6 % dimethylsulphoxide (DMSO), or supplemented with increasing concentrations of the internal calcium chelator, BAPTA-AM (100 µM, 200 µM, or 400 µM), prior to freezing at -80 °C. Platelets were tested fresh and following cryopreservation (n=8 per group). The phenotype and function of platelets was assessed using flow cytometry and thromboelastography. Statistical analysis was performed using a one-way ANOVA with *post-hoc* Bonferroni tests. A p value less than 0.05 was considered significant.

Results: Supplementation of platelets with BAPTA-AM prior to freezing improved platelet recovery in a dose response manner (400 µM: 84 ± 2%) compared to standard DMSO cryopreserved platelets (70 ± 4%). There was a loss of GPIbα, GPVI, and GPIIb/IIIa receptors on platelets following cryopreservation, which was rescued when platelets were supplemented with BAPTA-AM (400 µM: $p<0.0001$ for all). Platelet activation markers, such as phosphatidylserine and P-selectin, were externalised on platelets following cryopreservation. Addition of BAPTA-AM significantly reduced the externalisation of these markers (400 µM: $p<0.0001$ for both). Despite these changes, the clot forming ability of BAPTA-AM treated platelets was similar to standard DMSO cryopreserved platelets, as assessed by thromboelastography, forming clots at a faster rate than fresh platelets.

Conclusion: This study demonstrates that calcium plays a crucial role in mediating cryopreservation-induced changes to frozen platelets. The addition of the calcium chelator, BAPTA-AM, prior to cryopreservation reduces these alterations, improving platelet recovery and quality.

08.08

Preoperative intravenous iron did not reduce the need for blood transfusion in iron deficient patients undergoing major abdominal surgery: PREVENTT RCT Subgroup Analysis

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Background: The PREVENTT RCT showed that the use of preoperative intravenous iron versus placebo did not reduce the need for blood transfusion (up to 30-days) in patients with anaemia undergoing major abdominal surgery. While biomarkers of iron deficiency were not available to the study team prior to surgery, bloods were collected at both randomization and on the day of surgery, and later analysed by a centralised laboratory to facilitate a predefined subgroup analysis comparing outcomes in patients with iron deficiency anaemia to those without.
Aim: To reassess the primary endpoints of the PREVENTT RCT by preoperative ferritin (ng/mL) and transferrin saturation (TSAT%).
Methods: Heterogeneity of treatment effects were evaluated for the primary endpoints using a prespecified set of subgroup analyses based on the following categorisations of baseline ferritin or TSAT: ferritin ranges (<30, 30-<100, >100); baseline TSAT % (<20, >20) and combination thereof; ferritin and TSAT (ferritin <100 *OR* TSAT <20, ferritin >100 AND TSAT >20; ferritin <100 *AND* TSAT <20, ferritin >100 OR TSAT >20). For each subgroup analysis, a test of interaction (between the subgroup and treatment arm) was based on the likelihood ratio test. We also estimated a complimentary set of models where ferritin or TSAT were modelled continuously using restricted cubic splines, and similarly tested for interactions with treatment arm.
Results: While the subgroup specific treatment effect on the number of post-operative blood transfusions in patients with a baseline ferritin < 30 ng/ml suggested a benefit, the p- value for the overall test for interaction was 0.06 (Table 1). Furthermore, there was no evidence of heterogeneity of treatment effect based on the tests of interaction, for any other outcomes.

	Placebo	Active	IRR (95% CI)	p
Ferritin ng/ml < 30	0.5 ± 1.1	0.2 ± 0.5	0.45 (0.2 to 0.98)	0.06
Ferritin ng/ml 30 - 100	0.4 ± 0.9	0.7 ± 1.3	1.53 (0.75 to 3.1)	
Ferritin ng/ml ≥ 100	0.5 ± 0.8	0.5 ± 0.9	1.04 (0.64 to 1.7)	
TSAT% < 20	0.5 ± 1	0.5 ± 1	0.92 (0.6 to 1.4)	0.29
TSAT% ≥ 20	0.3 ± 0.7	0.4 ± 0.7	1.55 (0.63 to 3.8)	
Ferritin ng/ml < 100 OR TSAT% < 20	0.5 ± 1	0.5 ± 1	0.95 (0.63 to 1.43)	0.29
Ferritin ng/ml ≥ 100 and TSAT% ≥ 20	0.3 ± 0.6	0.4 ± 0.8	1.72 (0.66 to 4.51)	
Ferritin ng/ml < 100 AND TSAT% < 20	0.5 ± 1	0.4 ± 0.9	0.88 (0.49 to 1.55)	0.51
Ferritin ng/ml ≥ 100 or TSAT% ≥ 20	0.5 ± 0.8	0.5 ± 0.9	1.14 (0.69 to 1.89)	

Table 1: Within-group outcomes (number of blood transfusions up to 30 days post-surgery) are summarized as means and SDs. IRR = Incidence Rate Ratio estimated using negative binomial models. P-values are from the likelihood ratio test of the interaction between treatment group and the respective covariate.

Conclusions: The diagnosis of iron deficiency anaemia prior to major surgery did not predict heterogeneity in the treatment effect of intravenous iron on outcomes after major abdominal surgery.

08.09

Changing red blood cell (RBC) and platelet transfusion needs in myelodysplastic syndromes (MDS): A 15-year Australian population data-linkage study

Dr Allison Mo[1,2,3], *Professor Erica M Wood[1,2], Associate Professor Jake Shortt[2,4], Mr Ani Goswami[5], Ms Christine Quek[5], Associate Professor Zoe K McQuilten[1,2]*
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Aim: Anaemia and thrombocytopenia are common in MDS, and transfusions are frequently administered. Evidence guiding transfusion management, and data about Australian MDS transfusion practices, transfusion-related outcomes and changes over time with increasing access to disease-modifying therapies, remains sparse. We aimed to characterise the transfusion needs of MDS patients and explore transfusion-related outcomes.

Methods: Retrospective longitudinal cohort study including all patients with MDS/CMML admitted to Victorian hospitals from 2002-2017. Via data linkage of the Victorian Admissions Episode Dataset and Victorian Cancer Registry, transfusion episodes and outcome events (cardiac ischaemia/failure, transfusion reactions, bleeding) were analysed.

Results: 142,765 admissions involving 6771 patients were included (5970 MDS; 801 CMML). The cohort was elderly (>50% aged □70y). 66,068 (46.3%) admissions involved RBC transfusion, with median 3 admissions (IQR 1-10) per patient and median 14 days (IQR 14-33) between transfusions. 3433 (50.7%) of patients were RBC transfusion-dependent (TD) (□2 RBC transfusions within 16-weeks). From 2002-2017, the proportion of admissions involving RBC transfusion, median number of RBC transfusion admissions per patient, and rates of RBC-TD decreased. Cardiac events were common, and more frequent in RBC-TD patients (acute cardiac ischaemia 14.6% vs 10.3%, p<0.001; acute cardiac failure 27.3% vs 14.1%,p<0.001).

10,049 (7.0%) admissions involved platelet transfusion, increasing over time. Median time between platelet transfusions was 7 days (IQR 4-16). 2436 patients (36.0%) experienced bleeding, including 51.3% of platelet-transfused patients. The commonest bleeding site was gastrointestinal (n=1388, 20.5%). Intracranial bleeding occurred in 175 patients (2.6%).

Conclusion: This study highlights the high transfusion burden in MDS patients, and related adverse cardiac and bleeding outcomes. RBC transfusion requirements reduced over time but platelet transfusions increased; this may be related to changing MDS-related therapies or clinician practices. These data will help design future MDS transfusion trials, which should include quality-of-life and health economics outcomes, given the burden of transfusion on elderly patients.

08.10

Removal of HLA Class-I antigens from platelets: increasing platelet availability for refractory patients

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Aim: Antibodies to class-I human leukocyte antigens (HLA) are the leading cause of immune-related platelet refractoriness. HLA matching and restriction are often limited by donor availability. HLA removal may enable transfusion of refractory patients without HLA matching. This study examined the effects of HLA removal using citric acid on platelet quality and function.

Method: Apheresis platelets (n=10) were treated with saline or citric acid (pH 3.0), stored and tested on day 1, 5, and 7 post-collection. HLA antigens and platelet glycoproteins, viability, activation markers (CD62P and phosphatidylserine) and mitochondrial membrane potential (MMP) were assessed by flow cytometry. Platelet metabolism, aggregation, coagulation by thromboelastography (TEG), and reactivity with patient serum containing HLA antibodies were also assessed. Data were analysed using two-way repeated measures ANOVA or paired t-tests; $p<0.05$ considered significant.

Results: Acid treatment significantly reduced HLA-A, B, C ($p<0.0001$) and β2-microglobulin on the platelet surface ($p<0.0001$), as well as reactivity to patient serum antibodies ($p<0.0001$). However, acid treatment led to a significant reduction platelet content ($p<0.0001$). Acid treatment increased platelet metabolism, with increased glucose consumption ($p=0.009$) and lactate production ($p=0.001$), but decreased platelet viability and MMP ($p<0.0001$ and $p=0.001$). Surface CD41a and CD42b were significantly reduced ($p=0.007$ and $p=0.002$); CD61 was unchanged ($p=0.314$). Acid-treated platelets were more activated, with increased surface CD62P and phosphatidylserine exposure ($p<0.0001$ for both). Acid treatment blunted responsiveness to agonist stimulation, for both TRAP-6-induced CD62P exposure ($p=0.001$) and ADP-induced PAC-1 binding ($p<0.0001$). However, aggregation in response to collagen was significantly higher in acid-treated platelets ($p=0.001$), and there was a reduced time to clot formation ($p<0.0001$).

Conclusion: Acid treatment of platelets reduced HLA class-I antigen levels, but also reduced platelet content, with increased platelet metabolism and activation. However, the acid-treated platelets remained functional, and with further development, may become an alternative when HLA-matched platelets are not available.

9. HSANZ Free Communications

09.01

Real-world outcomes of patients with primary CNS lymphoma (PCNSL): a report from the Australasian Lymphoma Alliance (ALA).

Dr Maciej Tatarczuch[1], *Dr Katharine Lewis, Dr Ashray Gunjur, Dr Briony Shaw, Dr Michelle Poon, Dr Erin Paul, Dr Matthew Ku, Dr Mark Wong, Dr Ashley Beekman, Dr Michael Krigstein, Dr Pietro Di Caccio, Dr Joel Wight, Dr Caitlin Coombes, Dr Michael Gilbertson, Ms Amanda Tey, A/Prof Jake Shortt, Dr Chandramouli Nagarajan, Dr Maya Latimer, A/Prof Dipti Talaulikar, A/Prof Nada Hamad, Dr Sumita Ratnasingam, Dr Tara Cochrane, A/Prof Eliza Hawkes, Prof Chan Cheah, Prof Stephen Opat, Dr Gareth Gregory*
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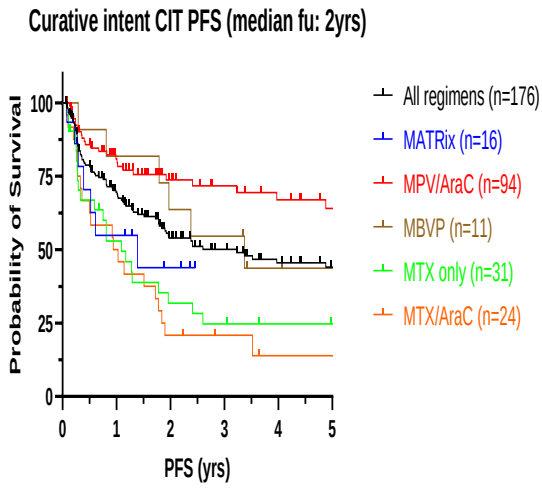
Aim: PCNSL is a rare and historically poor-prognostic disease predominant in older patients (median age: >60yo). MATRix and MPV/Ara-C (±rituximab) chemoimmunotherapy (CIT) trials have reported 2-year PFS and OS of 57-61% and 69-81% respectively. Our aim was to evaluate registry-reported outcomes of frontline CIT strategies employed at ALA sites.

Method: A retrospective study of consecutive, immunocompetent, adult PCNSL patients (WHO criteria: 2017) treated with curative-intent CIT, from 10 sites between 1/1/2009-31/12/2018. OS and PFS were calculated by Kaplan-Meier (log-rank) method and Cox-regression was used to perform univariable and multivariable analysis.

Results: 176 patients met WHO diagnostic criteria and received curative-intent CIT. Median age was 65 years (range 25-87) and 55% were male; ECOG PS ≥2 in 31% (N/A: 14%) and deep structure involvement in 64%. Five CIT regimens were employed: MATRix (n=16), R-MPV/Ara-C (n=94), MBVP+-R (n=11), MTX-only (n=31), MTX/Ara-C (n=24). Median total (cumulative) MTX dose was 17,500mg/m^2 (1,000-64,000) and 54% received Ara-C. Estimated 2-year PFS and OS for whole cohort were 54% (CI: 0.46-0.62) and 77% (CI: 0.70-0.83) respectively at median follow-up of 2 years. Neither WBRT (n=57) nor ASCT (n=13) conferred a survival advantage but addition of rituximab (n=153, 87%) was associated with improved PFS (p: 0.006, HR: 0.47, CI: 0.23-0.96). On multivariate analysis, type of induction CIT (p <0.001, HR: 1.507, CI: 1.408-1.606), total MTX dose (p <0.001, HR: 0.752, CI: 0.681-0.823) and Ara-C administration (p <0.001, HR: 0.348 CI: 0.520-0.644) were associated with improved PFS. Type of CIT (p= 0.006, HR: 1.388 CI 1.189-1.587) and total MTX dose (p= 0.003, HR: 0.758, CI: 0.665-0.851) were associated with improved OS.

Conclusion: Registry-reported outcomes of contemporary CIT induction for PCNSL are favourable when compared to published trials and historical regimens. PCNSL with contemporary treatment should no longer be considered an invariably poor-prognostic disease.



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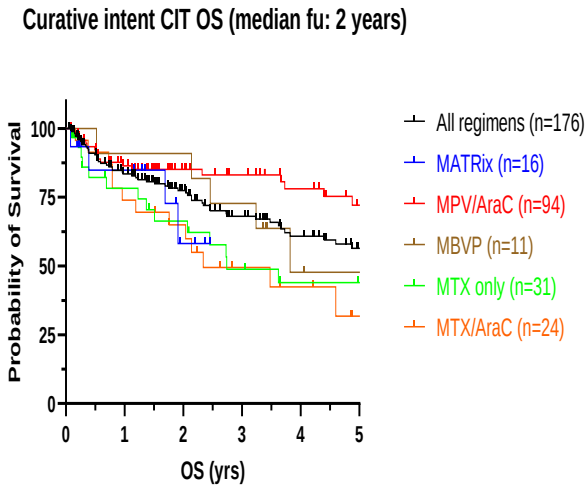

P-trend<0.0001

09.02

Intratumoural T-cells have a differential impact on FDG-PET parameters in Follicular Lymphoma

Dr Karthik Nath, *Soi-Cheng Law[1], Dipti Talaulikar[2], Muhammed B. Sabdia[1], Jay Gunawardana[1], Lilia M. de Long[1], Mohamed Shanavas[1], Hennes Tsang[1], Joshua W.D. Tobin[1], Sarah-Jane Halliday[3], Annette Hernandez[3], Donna Cross[3], Robert J. Bird[3], Sanjiv Jain[4], Colm Keane[1,3], Judith Trotman[5], Phillip Law[6], Maher K. Gandhi[1,3]*

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Aim: The prognostic impact of pre-therapy FDG-PET parameters TMTV (3D tumour burden of all involved sites) and SUV_{max} (highest FDG-uptake within a single lesion) in follicular lymphoma (FL) typically differs between R-CHOP/R-CVP versus Bendamustine-R/O. Recently we demonstrated the link between the tumour microenvironment (TME) and clinical outcomes in FL patients (Tobin, JCO, 2019). However, the relationship between intratumoural T-cells and PET parameters is unknown.

Methods: A comprehensive molecular and functional analysis was undertaken in 83 patients with *de-novo* Grade I-IIIa FL.

Results: Low intratumoural T-cell gene expression (by NanoString) was associated with ~6-fold higher TMTV. Consistent with this, FL nodes with increased malignant B-cell infiltration (by flow cytometry) showed high TMTV.
Next, to directly compare glucose-uptake between intratumoural B- and T-cells, a fluorescently labelled glucose analogue (2-NBDG) flow cytometric assay was performed. Surprisingly, glucose-uptake was higher in $CD4^+$ and $CD8^+$ non-malignant T-cells than in malignant B-cells. However, as B-cells made-up ~2/3^{rds} of total lymphocytes, they contributed most to overall glucose-uptake, demonstrating that TMTV reflects the burden of the malignant population.
To test SUV_{max}, we interrogated a unique subset of 12 patients in whom *pre-biopsy* PET scans were available. This allowed comparison of the TME gene expression profile of the excised node with its corresponding *pre-biopsy* SUV_{max}, thereby accounting for the impact of tumour spatial heterogeneity on SUV. Pre-biopsy SUV_{max} associated with *CD4* and *CD8A*, but not *CD19*.

Conclusion: We present, for the first time, a detailed characterization of the TME's role on FL PET parameters. TMTV best reflects the malignant FL B-cell burden, whereas intratumoural T-cells influence SUV_{max}. This may contribute to the contradictory results between prognostic roles of different PET parameters, particularly between short and long-term T-cell depleting chemoimmunotherapeutic regimens. The impact of glucose-uptake in intratumoural T-cells should be considered when interpreting pre-therapy FDG-PET in FL.

09.03

The impact of the gut microbiome on T cell immune reconstitution at the metataxonomic and metagenomic level following allogeneic hematopoietic stem cell transplantation.

Dr Salvatore Fiorenza[1], *Dr Jonathan Golob[1], Dr Samuel Minot[1], Dr Alyssa Sheih[1], Dr Sujatha Srinivasan[1], Dr Alexandre Hirayama[1], Dr Colleen Delaney[1], Dr Filippo Milano[1], Ms Aesha Vakil[1], Ms Tinh-Doan Phi[1], Ms Delaney Kirchmeier[1], Ms Erin Peterson[1], Dr David Fredricks[1], Dr Cameron Turtle[1]*
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Aim: In this study we aimed to show how whole genome sequencing (WGS) can complement 16S ribosomal RNA sequencing in providing insights into shared genetic elements, metabolic cooperation and sub-species heterogeneity within complex bacterial communities that exist following allogeneic haematopoietic stem cell transplantation (allo-HSCT). In particular, we aimed to identify the elements of the GM that are associated with T cell immune reconstitution (IR).

Method: We undertook a prospective analysis of changes in IR and the GM following allo-HSCT in 110 patients transplanted over six years at the Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance. We used Bayes regression analyses to identify associations of T cell IR with transplant outcomes. We used mixed-effects modelling to assess for interactions between 16S rRNA seq and IR and a novel beta-binomial regression analysis to identify associations between IR and the GM at the gene level identified by WGS.

Results: Recovery of mucosal associated invariant T (MAIT) cells and T regulatory (Treg) cells is inversely associated with acute GVHD severity. We then, for the first time, show the utility of 16S rRNA seq *and* WGS in the *same* dataset. 16S rRNA sequencing data revealed inverse associations between Treg reconstitution and Anaerotruncus colihominis – a firmicute reported that constrains immune checkpoint therapy[1]. WGS circumvented the diluting effect of sub-genus competition, revealing that *Clostridiodes difficile* and sub-species clades within *C. diff* are associated with Treg reconstitution – extending previous observations made in mouse models[2,3]. MAIT cell reconstitution was associated with known riboflavin-metabolising bacteria by 16S rRNA seq and WGS was able to precisely identify riboflavin-producing enzymatic complexes underpinning this association.

Conclusion: Our comprehensive, novel, dual-methodological analysis of T cell reconstitution at both the metataxonomic and metagenomic level thus illuminates avenues for understanding the GM post-allo-HSCT and identifying potential, microbial therapeutic manipulations in the peri-transplant period.

[1]Gopalakrishnan et al. Science, 2018.
[2] Atarashi et al. Nature, 2013.
[3] Arpaia et al. Nature, 2013.

09.04

The presence of cancer-associated gene mutations and Ph-associated rearrangements at the time of diagnosis of chronic-phase CML predict for inferior outcomes

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Background: A high incidence of mutated cancer-related genes at CML diagnosis was identified in selected chronic phase patients with poor outcomes compared to those with optimal outcomes. Furthermore, a novel variant class termed 'Ph-associated rearrangements', associated with the formation of the inciting Ph chromosome, also had a higher incidence in patients with inferior outcomes. However, the risk attributable to these mutational events at diagnosis has not been defined in unselected cohorts.

Aim: To assess the impact of genomic events in a cohort of consecutively treated patients at diagnosis of chronic phase CML.

Method: A hybridization capture sequencing method targeting genes implicated in myeloid and lymphoid malignancies was applied to diagnostic RNA of patients enrolled in the TIDEL II trial. Patients were treated with upfront imatinib with active intervention, dose escalation or nilotinib switch, primarily for lack of time-dependent molecular milestones. Damaging mutations in cancer-related genes and Ph-associated rearrangements were assessed. The influence of mutational events and other key clinical and demographic variables was evaluated on treatment outcome at 4 years.

Results: Interim analysis of 160/210 TIDEL II patients was performed. Thirty-three mutations with variant allele frequencies ≥5% were identified in 9 genes in 25 patients (16%). *ASXL1* was most frequently mutated (10% of all patients). Ph-associated rearrangements occurred in 25 patients (16%). The presence of any mutational event (cancer-gene mutation or Ph-associated rearrangement) was associated with a higher probability of progression to accelerated phase or blast crisis (25% vs. 2%, P=.02) at 4 years. Similarly, these events also predicted for *BCR-ABL1* kinase domain mutation development (18% vs. 2%, P<.001), MMR achievement (72% vs. 91%, P=.002) and MR4 achievement (34% vs 75%, P<.001).

Conclusion: Despite a proactive strategy for tyrosine kinase inhibitor switch and a higher imatinib starting dose, the presence of cancer-related gene mutations or Ph-associated events conferred inferior outcomes.

09.05

The Australian Aplastic Anaemia and other Related Bone Marrow Diseases Registry (AAR) – Treatment approaches in and outcomes of the idiopathic aplastic anaemia (iAA) cohort

Dr Lucy Fox[1,2], *Dr Xavier Badoux*[3], *Dr Ashish Bajel*[1], *Dr Pasquale Barbaro*[4], *A/Prof Merrole Cole-Sinclair*[5], *Professor Frank Firkin*[2], *Dr Cecily Forsyth*[6], *Ms Vanessa Fox*[2], *Professor John Gibson*[7], *Professor Divendra Hiwase*[8], *Dr Anna Johnston*[9], *A/Prof Zoe McQuilten*[2,10], *Dr Anthony Mills*[11], *Dr Sue Morgan*[12], *Professor Stephen Opat*[10], *Dr Fernando Roncolato*[3], *A/Prof Stephen Ting*[13], *Professor Jeff Szer*[1], *Mr Neil Waters*[2], *Dr Daniela Zantomio*[14], *Professor Erica Wood*[2,10]

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Aim: Idiopathic aplastic anaemia (iAA) is an uncommon bone marrow failure (BMF) disorder. Treatment options depend upon age and allogeneic stem cell transplant (alloSCT) donor availability. The AAR aims to capture all Australian patients with BMF to describe treatment approaches and patient outcomes.

Method: Analysis of national AAR dataset for iAA patient characteristics, treatment practices and outcomes.

Results: Of the 208 patients enrolled on the AAR at April 2021, 156 evaluable patients had a working diagnosis of iAA. Median age was 37 years (range 2-94) with male:female ratio 1:1. Upfront treatment approaches included ATG(horse)/cyclosporin (n=87), alloSCT (n=15, all aged <40 years), alternative immunosuppressive/other combination therapy (n=29) and transfusion support only (n=2). Nine patients had non-severe iAA not requiring treatment and 14 patients had insufficient data available. 35 patients underwent alloSCT, including as second-line (n=14), third-line (n=5) and fourth-line therapy(n=1); 3 patients underwent 2 allografts. 22% (34/156) patients have died, with median age at death of 61 years (range 13-94) and median time from diagnosis to death of 12 months (range 3 weeks-66 months). Cause of death was mostly related to iAA, including due to infection (23/35,66%), haemorrhage(n=5), and acute myeloid leukaemia(n=4). 29%(10/35) patients who underwent alloSCT have died, with median age at death of 37 years (range13-67) and median time to death following alloSCT of 54 days(range 4-211); none of the deceased patients had undergone upfront allograft from a matched sibling donor. 28/33(85%) deceased patients with FBE results available had an FBE performed within the last 3 days of life, including 14 patients on the day of death, likely reflecting young age and the often acute nature of the final illness.

Conclusion: iAA is associated with significant mortality, with death due to infection being most common. Treatment decisions are complex. Analysis of national AAR data will inform optimal management strategies.

09.06

Targeting BclxL with panobinostat mitigates Mcl1 chemoresistance in Multiple Myeloma

Dr Ioanna Savvidou[1], *Dr Tiffany Khong*[1], *Dr Irena Carmichael*[2], *Dr Jaynish Shah*[1], *Prof Andrew Spencer*[1,3]
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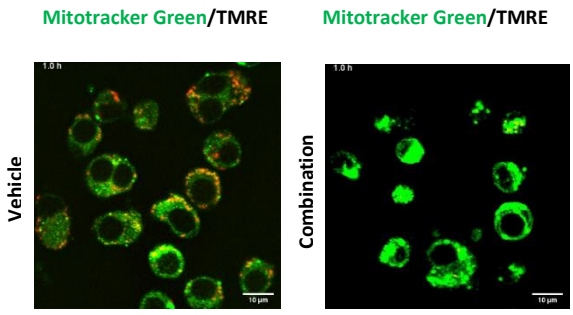
Aim: Despite the adoption of novel therapeutic modalities, Multiple Myeloma (MM) remains incurable. The Bcl2 inhibitor Venetoclax is active in several haematologic malignancies, but the benefits in MM patients are limited to those with the t(11;14) and/or high Bcl2 expression. These results underscore the significance of Bcl2 alternative anti-apoptotic proteins (Mcl1 and BclxL) for the survival of myeloma cells.

Method: We validated the anti-MM effect of the Mcl1 inhibitor S63845 both *in vitro* utilising 12 human myeloma cell lines (HMCL) and *ex vivo* against n=30 primary MM tumours. Comparative analysis of RNAseq between S63845 sensitive and resistant tumours was undertaken to identify candidate proteins that potentially modulate resistance to S63845. Treatment with S63845 and rationally selected combination partners was further evaluated *in vitro*, *ex vivo* and *in vivo* with flow cytometry, immunoblotting and live imaging mitochondria fitness monitoring.

Results: RNAseq identified BclxL and Myc as potential mediators of resistance to S63845. The S63845 resistant HMCL U266 and primary tumours were treated with S63845 combined with the BclxL inhibitor A1331852. Combined treatment of U266 demonstrated a high Bliss synergy score of 63 and induced synergistic killing of 80% of the primary tumours. Dual inhibition induced an 80% drop in intracellular ATP at 4h with an increase in active Caspases 9 and 8 (4.5 and 5 fold, respectively). Similarly, the combination induced a 78% drop in mitochondrial transmembrane potential (TMRE intensity) by 4h with live imaging revealing striking mitochondrial damage as early as 40 minutes after exposure (figure). These changes were associated with a reduction of both Mcl1 and BclxL proteins and Bim and Bid protein levels. No changes were seen in the level of Bcl2, Bak or Bax protein expression. The combination of S63845 and A1331852 in healthy NSG mice at 12.5mg/kg proved lethal due to hepatotoxicity, arguing against the clinical utility of such an approach. However, this observed anti-MM synergistic activity was recapitulated when S63845 was combined with the already approved anti-MM therapeutic panobinostat, with the induction of a significant reduction in both BclxL and Myc protein levels at 24h and synergistic killing of 56% of primary tumours.

Conclusion: High BclxL and Myc expression correlates with resistance to the Mcl1 inhibitor S63845. A combinatorial approach targeting Mcl1 and Bclxl induced immediate and significant anti-MM effect both *in vitro* and *ex vivo* but proved to be toxic *in vivo*. Combination of the anti-MM therapeutic panobinostat in combination with S635845 recapitulated the anti-MM activity seen with A1331852 and warrants further evaluation.



09.07

Acquired mutations within the JAK2 kinase domain confer resistance to JAK inhibitors in in vitro models of acute lymphoblastic leukaemia

Ms Charlotte Downes[1,2], *Dr Barbara McClure*[1,3], *Dr John Bruning*[4], *Dr James Breen*[3,5,6], *Ms Jacqueline Rehn*[1,3], *Dr David Yeung*[1,3,7], *Prof Deborah White*[1,2,3,8]
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Introduction: *JAK2*-rearrangements (*JAK2*r) are associated with poor prognosis in B-cell acute lymphoblastic leukaemia (B-ALL). Outcomes may be improved by incorporating targeted therapies and a clinical trial is currently assessing the only FDA-approved JAK1/2 inhibitor, ruxolitinib. We predict that a subset of patients will develop resistance to ruxolitinib.

Aim: Investigate mechanisms of acquired JAK inhibitor resistance in *JAK2*r ALL to inform monitoring and aversion of resistance.

Method: *JAK2*r B-ALL was modelled in the pro-B cell line, Ba/F3, by expressing a high-risk B-ALL *JAK2* fusion gene. Acquired ruxolitinib resistance in three independent cell lines was achieved following dose escalation to a clinically relevant dose (1 µM). Sanger sequencing revealed each resistant line had acquired a different *JAK2* kinase domain mutation. Computational modelling of JAK2 mutations and their influence on ruxolitinib binding was performed using ICM-Pro (Molsoft L.C.C.). Therapeutic sensitives were assessed by flow cytometry following staining with Fixable Aqua Dead Cell Stain (Invitrogen) and Annexin V-PE.

Results: In addition to the identification of two known ruxolitinib-resistant mutations, *JAK2* p.Y931C and p.L983F, a novel p.G993A mutation was identified. All mutations localised to the JAK2 ATP/ruxolitinib binding site. Computational modelling suggested that JAK2 p.L983F sterically hinders ruxolitinib binding, while JAK2 p.Y931C reduces ruxolitinib binding affinity by loss of stacking interactions. The novel JAK2 p.G993A mutation is predicted to alter DFG-loop dynamics by stabilising the JAK2 activation loop. All three ruxolitinib-resistant mutations conferred resistance to all tested type-I JAK inhibitors. *JAK2* p.G993A-mutant Ba/F3 cells were also resistant to the type-II JAK inhibitor, CHZ-868, suggesting that sequential use of JAK inhibitors may not overcome resistance.

Conclusion: *JAK2*r ALL is a high-risk disease that may be amenable to targeted inhibition to improve outcomes. We identified critical residues within the *JAK2* ATP-binding site that if mutated may confer resistance to JAK inhibitors anticipated to enter ALL therapeutics.

09.08

Live cell imaging demonstrates increased immune synapse formation by T cells from B-ALL patients in the presence of blinatumomab

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Aim: The CD3/CD19 bispecific T cell engager blinatumomab (blin) is effective for the treatment of relapsed or refractory B cell acute lymphoblastic leukaemia (B-ALL). Total CD8 T cell numbers at the time of treatment have been associated with a higher likelihood of response. However, until now, no studies of patient T cell function have been reported. We hypothesised that response to blin would be dependent on pre-treatment T cell fitness as measured by their ability to form synapses with CD19+ targets in the presence of blin.

Method: Live cell video microscopy was used to assess synapse formation by T cells in 30 patients with B-ALL who were enrolled in a prospective study of untreated adult B-ALL (Australasia Leukaemia and Lymphoma Group ALL08 Trial) in which blin was used as part of induction therapy following a pre-phase of steroids and low-intensity chemotherapy.

Results: Baseline T cell activity against a CD19-expressing B cell tumour target in the presence of blin showed a 4 fold increase in immune synapse formation compared to untreated controls ($p=0.0105$). The duration of T cell attachment to the CD19-expressing B cell tumour target was also increased in the presence of blin. When correlated to MRD response status in the 9 patients with outcome data available, those who achieved MRD negative status after blin therapy had an average of a 3.5 fold increase in synapse formation (compared against synapses in the absence of blin), whereas those who had MRD persistence had a 1.7 fold increase in blin-induced synapses.

Conclusion: Our data demonstrate that live cell imaging can be used to quantify the ability of T cells to form blin-induced synapses with CD19 targets and suggest that the degree of synapse formation may be correlated with post-blin disease response. Further correlative data with MRD responses will be presented.

09.09

Clinical outcomes between induction regimens for mixed phenotypic acute leukemia (MPAL) in adults.

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Aim: While outcomes in MPAL are well described in children and mixed cohorts, the outcome of MPAL in adults as an isolated cohort is relatively poorly described. We examined the clinical outcomes for patients based upon induction chemotherapy received.

Method: A multi-site, retrospective cohort study was conducted in 3 Victorian tertiary hospitals from January 2000 to December 2020. All patients ≥18 years old who meet the WHO 2008 diagnostic criteria for MPAL, were identified by matching data from clinical records with laboratory databases. Induction regimens were categorised into acute myeloid leukemia (AML)-like and acute lymphoblastic leukemia (ALL)-like chemotherapy. The outcomes of interest were clinical remission (CR), allogeneic hematopoietic stem cell transplantation (alloHSCT), overall survival (OS) and progression-free survival (PFS). A univariate descriptive statistics analysis was conducted using a non-parametric procedure, and Kaplan-Meier (KM) method was used to estimate OS.

Results: Among the 21 MPAL patients, 7 (33.3%) received ALL-like chemotherapy, 11 (52.4%) received AML-like chemotherapy, and 3 (14.3%) were untreated. The CR rates following induction (ALL-like 85% vs AML-like 81%) and alloHSCT rates (ALL-like 85.7% vs AML-like 72.7%) were similar. The whole group median OS was 42.6 months (0.4-144.5 months) with a median PFS of 22.5 months (0.4-28.1 months). Patients who received ALL-like therapy had a lower risk of death (HR 0.67) or progression (HR 0.53) than those receiving AML-like therapy. The median OS was NR vs 3.8 years (p = 0.61, Figure1A) with a median PFS of NR vs 2.3 years (p=0.48. Figure1B). Although this was statistically insignificant, this is aligned with current literature suggesting better treatment outcomes from ALL-like therapy [1-4].

Conclusion: Despite there being no difference in CR or alloHSCT rates based upon treatment regimen there appears to be an advantage in survival and progression for ALL-type therapy. This requires assessment in a larger cohort.

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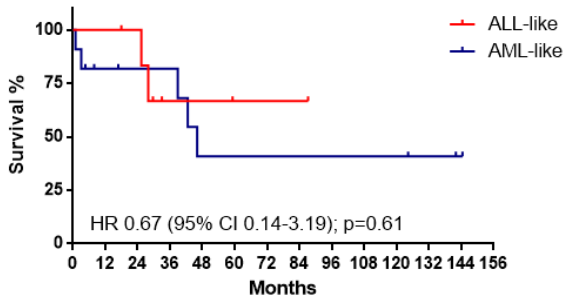

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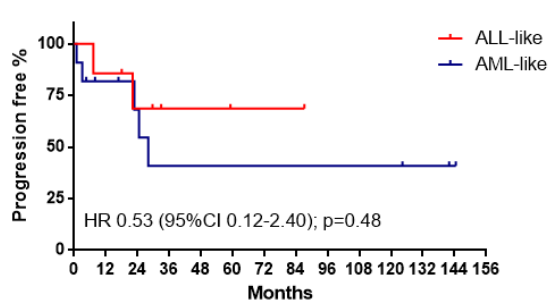

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09.10

Assessment of risk of relapse in childhood B-ALL is improved by a risk score including IKZF1 and CRLF2 microdeletions

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Aim: To evaluate a risk score based on MRD; NCI risk and microdeletions detected by qPCR or MLPA

Background: Children with acute lymphoblastic leukaemia (ALL) are split into treatment risk groups largely on the basis Minimal Residual Disease (MRD) levels at the end of induction, with high risk patients receiving more intensive therapy. However, some relapses still occur in non-high risk patients with low or no detectable MRD, particularly in older children (>10 years) or those with ALL with IKZF1 or P2RY8-CRLF2 deletions.

Method: Microdeletions were identified by real-time quantitative qPCR (IKZF1 2-7, IKZF1 2-8, IKZF1 4-7, IKZF1 4-8 and P2RY8-CRLF2) and by MLPA in 471 ANZCHOG Study 8 patients classified as no-high risk by MRD. Risk Scores were determined as the total of 1 point for a deletion(s), 1 for MRD>$5x10^{-5}$ at end of induction and I point for age>10 or white cell count >50.

Results: Microdeletions were detected in 8% of patients by qPCR (versus 15% by MLPA which also detects whole IKZF1 gene loss and IGH-CRLF2). A high PCR risk score (RS2 or RS3) identified 10% of patients as high risk (vs 13% MLPA high risk score), with an incidence of 44% (47%) relapses and 30% (27%) deaths. With both qPCR and MLPA based scoring systems, half of the patients (52% and 50%) did not have any of the risk factors and the relapse rates in these RS0 patients were 7% or 6% with 2% or 1% mortality.

Conclusion: A new risk score based on MRD, age and IKZF1 and CRLF2 deletions improves risk of relapse assessment. Risk scores based on qPCR deletion testing are rapid and low cost while MLPA assessment is more comprehensive.

09.11

Genomic characterisation of ZNF384-rearranged B-cell acute lymphoblastic leukaemia reveals targetable pathways.

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Aim: Characterising the genomic landscape of *ZNF384*-rearranged (*ZNF384*r) B-cell acute lymphoblastic leukaemia (B-ALL) will reveal subtype specific genomic alterations and define targetable pathways for assessment in precision therapeutic approaches.

Method: Philadelphia chromosome-negative B-ALL samples (n=487) were transcriptionally sequenced to identify fusion genes and single nucleotide variants (SNV), and gene deletions were detected by multiplex ligation-dependent probe amplification. Signalling pathways were assessed on the *EP300-ZNF384* driven human JIH-5 cell line by intracellular flow cytometry of STAT1/3/5 phosphorylation in the presence or absence of inhibitors.

Results: Transcriptomic sequencing identified *ZNF384*r in 3.7% (18/487) of Ph-neg B-ALL at diagnosis (comprising children 1.4% (3/210), adolescent young adults 6.1% (10/165), adults 4.5% (5/112)). The 5'-partners identified were *EP300* (72%, 13/18), *TCF3* (17%, 3/18), *ARID1B* (5.6%, 1/18) and *CREBBP* (5.6%, 1/18). IKZF1, RB1, CDKN2A, and PAX5 deletions (7% each, 1/14) occurred less frequently than deletions in ETV6 (35.6%, 5/14), BTG (21.4%, 3/14) and CDKN2B (21.4%, 3/14). SNVs were detected in *RAS* 27.8% (5/18), *PTPN11* (5.6%, 1/18), *JAK2* (5.6%, 1/18) and *CREBBP* (11.1%, 2/18). In relapse samples *EP300* or *TCF3* were the most common fusion partner, (37.5%, 3/8), in addition to 12.5% (1/8) *TAF15* and 12.5% *CREBBP*. Upregulation of *CLCF1*, *CXCL2*, *FLT3*, *STAT2*, *ICAM2*, *MMP11* and *SPKH1* gene expression was detected in *ZNF384*r B-ALL. An *in vitro* model of *ZNF384*r B-ALL demonstrated intrinsic phosphorylation of STAT3, (consistent with JAK/STAT signalling upregulation observed in *ZNF384*r B-ALL Gene-set enrichment analysis), but not STAT1 or STAT5. Dasatinib and ruxolitinib were unable to abrogate STAT3 phosphorylation, while dasatinib reduced JIH-5 total tyrosine-phosphorylation. Pathways involved in *ZNF384*-fusions are currently under investigation.

Conclusion: We have characterised the transcriptome of one of the largest *ZNF384*r B-ALL cohorts and have revealed subtype specific targets warranting investigation for future precision approaches to therapy.

09.12

Early acute chemotherapy related toxicity in AYA ALL patients treated on a paediatric protocol - Results of the Australasian Leukaemia and Lymphoma Group (ALLG) ALL06 study

Dr Eleanor Cook[1], *Dr Toby Trahair*[1,2], *Dr Matthew Greenwood*[3,4], *Mr Kenneth Bradstock*[5], *Dr Luciano Dalla Pozza*[6], *Dr Andrew Wei*[7,8], *Dr Michael Osborn*[9], *Dr John Kwan*[10], *Dr Sally Mapp*[11,12], *Ashlee Burt*[13], *Amanda Jager*[13], *Aoife Dunne*[13], *Chris Frampton*[14]

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Aim: Adolescent and young adult (AYA) patients with acute lymphoblastic leukaemia (ALL) have improved survival when treated with paediatric-based treatment. Initial ALL treatment carries a significant risk of severe, life-threatening, treatment related toxicities (TRT). To understand the incidence of early TRT in AYA ALL patients, we examined adverse (AE) and severe adverse events (SAE) during protocol of the ALLG ALL6 clinical trial.

Method: AYA patients aged 15-40 years with newly diagnosed ALL were treated across 15 Australian centres from 2012-2020. ALL6 was a single arm study designed to assess the deliverability of a paediatric protocol (BFM 2000) in AYA ALL. A secondary endpoint was to examine TRT.

Results: Eighty six patients were registered and 82 patients were enrolled. There were three treatment related deaths (3.7%) during induction (1 sepsis, 1 thrombosis, 1 pancreatitis). SAEs occurred at a higher rate during consolidation (61% of patients experiencing ≥1 SAE). Infectious complications were common in consolidation with 36 SAEs due to febrile neutropenia and 16 due to sepsis, other infectious complications (including meningitis) and fever. Pancreatitis occurred in 2 patients (incidence 2.4%). Thromboembolism (≥Grade 2) occurred in 13 patients (incidence 15.9%), a higher rate than a matched paediatric population (3.8%). One patient withdrew from the trial after consolidation due to unacceptable toxicity.

Conclusion: AYA ALL patients can be successfully treated with paediatric regimens, but the incidence of early toxicity is high. The early treatment related death rate in the AYA population (3.7%) was higher than documented in paediatric trials. High rates of myelosuppression related TRTs during consolidation suggest that substitution of chemotherapy with blinatumomab may have a role in AYA ALL treatment.

09.13

A novel microRNA biomarker and therapeutic target for MDM2 inhibition in acute myeloid leukemia

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Aim: Pharmacological inhibition of MDM2/4, which activates the critical tumour suppressor p53, has been investigated for the treatment of a variety of cancers. This approach may be particularly effective in acute myeloid leukaemia (AML) where, unlike most solid cancers, the vast majority of malignancies express wildtype p53. While early clinical trials of MDM2 inhibitors have shown promise in this group, responses have been confined to largely molecularly undefined patients, indicating that new biomarkers and optimised treatment strategies are needed. We previously reported that the microRNA miR-10a is strongly overexpressed in a significant subset of AML patients, and is predicted to directly regulate several p53-related gene targets. We therefore aimed in the current study to investigate the potential of miR-10a as a therapeutic target and predictive biomarker for MDM2 inhibition in AML.

Method: We correlated the expression of miR-10a's targets to sensitivity to MDM2 inhibitor DS-3032b in 38 primary AML cell lines. We further correlated the expression of miR-10a itself to outcome in three independent AML cohorts totalling 300 cytogenetically-normal cytarabine-treated AML patients. Finally, we investigated the ability of a miR-10a inhibitor to sensitize AML cells to MDM2 inhibitor + cytarabine *in vitro* and *in vivo*.

Results: The expression of both miR-10a and its downstream targets were strongly predictive of MDM2 inhibitor sensitivity in cell lines, primary AML specimens treated *ex vivo*, and also correlated to response in patients treated with both MDM2 inhibitor and cytarabine-based chemotherapy. Furthermore, inhibition of miR-10a induced strong synergy between MDM2 inhibitor Nutlin-3a and cytarabine in both *in vitro* and *in vivo* AML models.

Conclusion: Together these findings demonstrate that miR-10a may be useful as both a biomarker to identify patients most likely to respond to cytarabine+MDM2 inhibition and also a druggable target to increase their efficacy.

09.14

Exploratory analysis of the efficacy and safety of CPX-351 versus 7+3 by European LeukemiaNet 2017 risk groups in a phase 3 study of older adults with high-risk/secondary AML

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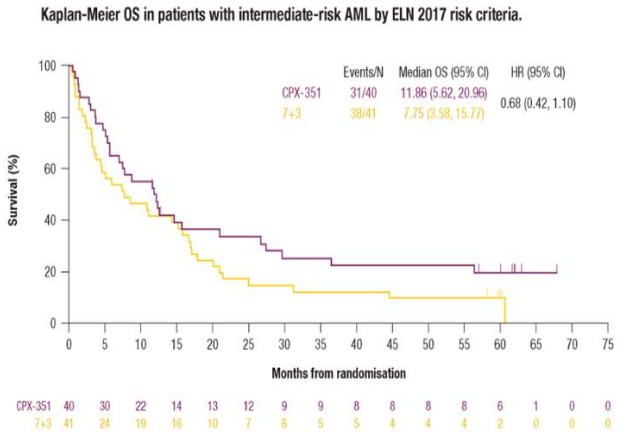
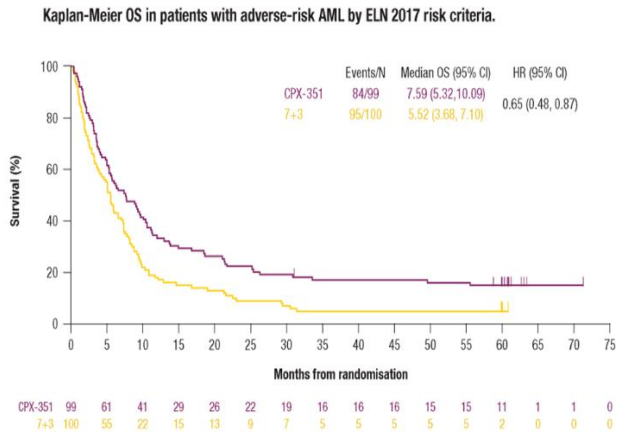
Aim: CPX-351 (Europe: Vyxeos® Liposomal; US: Vyxeos®) is approved by the EMA and US FDA for adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes based on a phase 3 study (NCT01696084) in 309 patients aged 60–75 years with newly diagnosed high-risk/secondary AML. This *post hoc* analysis of the phase 3 final 5-year data evaluated outcomes by European LeukemiaNet 2017 risk subgroups.

Method: Patients were randomised 1:1 to receive 1–2 induction cycles of CPX-351 or 7+3. Patients achieving complete remission (CR) or CR with incomplete platelet or neutrophil recovery (CRi) could receive up to 2 consolidation cycles.

Results: Of evaluable patients (CPX-351: n=149/153; 7+3: n=148/156), 10 (7%) and 7 (5%) had favourable-risk AML, 40 (27%) and 41 (28%) had intermediate-risk AML, and 99 (66%) and 100 (68%) had adverse-risk AML, respectively. CR+CRi rate was 58% with CPX-351 versus 39% with 7+3 for intermediate-risk AML and 41% versus 26% for adverse-risk AML. Median OS was longer with CPX-351 for both intermediate- and adverse-risk AML (**Figure**). For intermediate-risk AML, HCT rate was 35% with CPX-351 versus 34% with 7+3; median OS landmarked from the HCT date was not reached versus 13.6 months (HR=0.45 [95% CI: 0.16, 1.22]). For adverse-risk AML, HCT rate was 32% with CPX-351 versus 24% with 7+3; median OS landmarked from the HCT date was 43.1 versus 7.1 months (HR=0.49 [95% CI: 0.25, 0.95]). Mortality rate by Day 60 was 13% with CPX-351 versus 20% with 7+3 for intermediate-risk AML and 16% versus 25% for adverse-risk AML. The most common adverse events for both intermediate- and adverse-risk AML were febrile neutropenia, nausea, and diarrhoea.

Conclusion: CPX-351 improved median OS and post-HCT outcomes versus 7+3 in patients with intermediate- or adverse-risk AML by European LeukemiaNet 2017 criteria, with a safety profile consistent with that of 7+3.





09.15

Rapid T-cell recovery is associated with clearance of viraemia in patients administered third-party virus specific T cells (VSTs) at time of first-line therapy for infections post-allogeneic stem cell transplant (aHSCT)

Dr Wei Jiang[1,2,4], *Dr Ellis Patrick[1,2], Mr Adam Chan[2], Dr Selmir Avdic[1,2,3], Dr Leighton Clancy[1,3], Ms Janine Street[1,3], Mr Suat Dervish[1], Professor David Ritchie[5,7], Dr Adrian Selim[5,7], Professor Peter Shaw[6], Dr Caroline Margaret Bateman[1,6], Professor David Gottlieb[1,2,3,4], Associate Professor Emily Blyth[1,2,3,4]*
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Aim: To assess dynamics of immune reconstitution in recipients of third-party VSTs early in the course of viral infection following aHSCT**.**

Method: Epstein-Barr virus (EBV) and cytomegalovirus (CMV)-specific VSTs were administered to aHSCT recipients within 7 days of commencing antiviral treatment for these viruses. Multiparameter flow immunophenotyping was performed on post-infusion peripheral blood samples using a custom panel of 20 antibody markers covering 32 cell populations, identifying innate and adaptive subsets with a focus on T-cell subsets and activation markers. Viral antigen specificity in T-cell populations was assessed using virus-specific iTAg MHC class I tetramers where available based on VST and patient HLA-typing. Data was acquired using a BD FACSymphony flow cytometer. Immune reconstitution was assessed to 6 months post-last VST infusion.

Results: Thirty patients were treated; clinical results have been presented previously. 28/30 patients achieved a complete virological response (CR), defined as undetectable viral load by quantitative PCR by a median of 25 days post-infusion (range 10-161) without significant toxicity. Cytometry was performed on 162 post-infusion samples at multiple timepoints in 25 patients. $CD8^+$ T-cell expansion (median pre-infusion: 0.31 x 10^9/L, 100-day post-infusion: 0.72 x10^9/L) was associated with control of viraemia. The predominant subset within both $CD8^+$ and $CD4^+$ populations was $CD45RA^{neg}CD62L^{neg}$ effector memory cells, with an increase over time in $CD8^+$ $CD45RA^{pos}CD62L^{neg}$ terminally differentiated effector memory cells. 12/19 patients tested with CMV/EBV-specific tetramers showed a rapid rise of virus-specific T-cells to between 1-13% of $CD8^+$ T-cells, corresponding with virological CR, and persistence of these cells 6 months post-infusion. The 2 patients who didn't achieve CR showed poor recovery of adaptive immunity, with dominance of innate effectors.

Conclusion: Early infusion of VSTs to treat infection post-aHSCT was associated with rapid reconstitution of immunity that correlated with complete virological clearance. The immunophenotyping in this study will inform a randomised trial that is underway, comparing VSTs with antivirals to standard-of-care antivirals alone, to confirm clinical benefit.

09.16

Omission or reduction of day 11 methotrexate due to toxicity is associated with poorer outcomes in fludarabine, melphalan and anti-thymocyte globulin reduced intensity conditioning allogeneic stem cell transplantation.

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Background: Anti-thymocyte globulin (ATG) has lowered the incidence of chronic graft versus host disease (GVHD) in reduced intensity conditioning allogeneic stem cell transplantation (RIC-alloSCT). Methotrexate (MTX) is universally utilised as GVHD prophylaxis but dose-reduction is often required due to toxicities. The effects of this on RIC-alloSCT outcomes is not fully described. We conducted a retrospective analysis of the consequences of unplanned day 11 (D11) MTX dose-reduction or omission in RIC-alloSCT with ATG.

Method: Between 2015 to 2020, all patients undergoing RIC-alloSCT with fludarabine, melphalan (FluMel) and ATG (Thymoglobulin® 4.5mg/kg) from a human leukocyte antigen-matched unrelated donor scheduled to receive MTX (15mg/m2 on day1, 10mg/m2 on day 3, 6, and 11) in combination with cyclosporin for GVHD prophylaxis were identified. Demographic information, disease characteristics, GVHD incidence and survival were analysed.

Results: Of 93 patients identified, 33% (n=31) required MTX-dose reduction. Twenty three patients (25%) had D11 MTX omitted (15%) or dose-reduced (10%) with severe mucositis being the primary cause (70%). Patient, disease and transplant characteristics were similar. Comparing MTX D11 dose omission/reduction vs no reduction groups, at 1-year, overall survival (48% vs 71%; *P*=0.0147) (HR 3.2; 95% CI 1.3-8) and relapse free survival (RFS) (42.9% vs 66.1%; *P*=0.0187) (HR 2.8; 95% CI 1.2-6.7) were poorer due to higher non-relapse mortality (NRM) (46% vs 12%; *P*=0.0008)**.** There was no difference in the cumulative incidence of relapse (28% vs 17%, *P*=0.326), acute and chronic GVHD (30% vs 43%, *P*=0.211; 43% vs 42%, *P*=0.930) and 1-year GVHD RFS (29% vs 34%, *P*=0.212) were similar. Epstein-Barr virus reactivation requiring treatment was more common (57% vs 16%, *P*=0.0006) (OR 6.8; 95% CI 3.2-18.8).

Conclusion: In this study, unplanned day 11 MTX dose-reduction in FluMel ATG RIC-alloSCT is associated with poorer survival but at no increased risk of relapse disease or GVHD.

09.17

Intensive AML induction by the ALLG consensus approach results in excellent medium-term outcomes: a single-centre study

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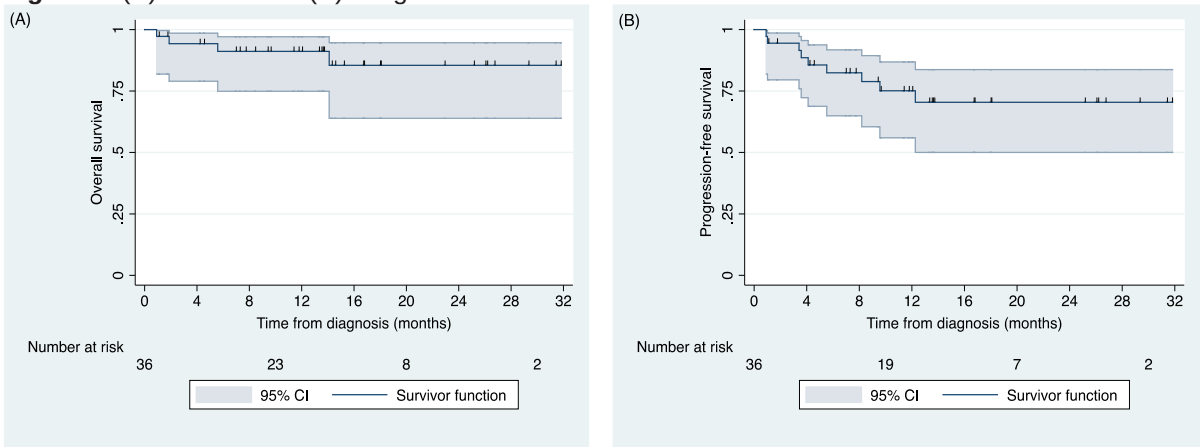
Aim: After a 15-year hiatus, Monash Health resumed intensive acute leukaemia inductions from mid-2018. In order to align with future co-operative group studies, we harmonised our induction/consolidation strategy with the HOVON-group and RATIFY-protocols as suggested by the ALLG Leukaemia Working Party. This incorporates a 7+3-based double-induction (with induction #2 offered if adverse ELN risk AML and/or unsatisfactory induction #1 response) followed by 3-4 cycles of high-dose cytarabine consolidation.

Method: All patients with newly-diagnosed AML (ND-AML) treated with intensive induction from Aug-18 to Apr-21 were included. Clinical characteristics, treatments & outcomes were analysed.

Results: A total of 36 patients (out of 43, 84%) age < 70 with ND-AML received intensive induction. Median age was 48 years (range: 22-69) and 39% were female. 31 (86%) had *de novo* AML with ELN risk strata: favourable (33%); intermediate (45%); adverse (22%)**.** 7+3-induction (cytarabine 100mg/m^2 (n=9) or 200mg/m^2 (n=27) + idarubicin 12mg/m^2) +/- midostaurin (for *FLT3*-mutated AML; n=11) was delivered in all patients. The composite CR+CRi rate was 94% (95%CI: 81%-99%). Two patients received induction #2 for adverse ELN risk disease. 29 patients (81%) proceeded to receive high-dose cytarabine consolidation; 21 received ≥3 cycles. 7 (19%) received allogeneic SCT in CR1, 3 (8%) based on adverse ELN risk and 4 (11%) with intermediate ELN risk plus a permissive donor and/or suboptimal MRD response. Median LOS for induction was 30d (range: 22-55) with a 22% ICU admission rate; whereas median LOS and ICU admission rate per consolidation cycle were lower; ranging from 10-17d and 8-10%. With a median follow-up of 13.5 months (range: 0.6-31.8), 4 patients had died (1 induction death, 3 R/R AML) and a further 5 had haematologic relapse. Estimated 2-year OS and PFS were 85% (95%CI: 63%-95%) and 70% (95%CI: 50%-84%), respectively (**Figure 1**).

Conclusion: The application of the ALLG consensus approach for intensive AML induction at Monash yields excellent remission rates and provides an appropriate platform for participation in future co-operative group clinical trials.

Figure 1. (A) Overall and (B) Progression-free survival of the Monash intensive AML cohort



09.18

Follow-up of patients with FLT3-mutated relapsed or refractory acute myeloid leukemia in the phase 3 ADMIRAL trial

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Aim: A follow-up of ADMIRAL assessed long-term survivors, transplant (HSCT) outcomes, and gilteritinib safety beyond 1 year.

Method: A data cut was performed 2 years after the primary analysis. Patients living without relapse, HSCT outcomes, and adverse events of interest (AEIs) in Years 1 (≤12 months) and 2 (>12 months) of gilteritinib therapy were evaluated.

Results: As of September 20, 2020, 17% (n=63/371) of ITT patients were alive (gilteritinib, n=49; SC, n=14); 16 gilteritinib-arm patients remained on treatment and 26 gilteritinib-arm patients were alive without relapse (median follow-up, 37.1 months). Of these 26 patients, 18 underwent HSCT, 16 received post-HSCT gilteritinib therapy, and 19 continued gilteritinib beyond 1 year and remained in CR.

Of the 371 ITT patients, 83 (22%) underwent on-study HSCT (gilteritinib, n=64; SC, n=19), with similar pre-HSCT CRc rates across arms (gilteritinib: 63%; SC: 58%). Forty of 64 (63%) gilteritinib-arm patients received post-HSCT gilteritinib maintenance after pre-HSCT CRc; the 24-month relapse rate in patients who resumed gilteritinib was 19%.

Cumulative 24-month relapse rates in gilteritinib-arm patients after pre-HSCT CR and CRc were 20% and 45%, respectively. Median post-HSCT overall survival was similar in gilteritinib and SC arms (16.1 and 15.3 months, respectively; HR=1.076; 95% CI: 0.536, 2.160).

Most common AEIs during Years 1 and 2 of gilteritinib therapy were elevated ALT/AST levels; AEI incidences declined in Year 2. Year 2 cardiac AEIs were nonfatal cardiorespiratory arrest (n=1) and ventricular tachycardia (n=1). Single cases of differentiation syndrome and cutaneous squamous cell carcinoma occurred.

Conclusion: A high proportion of gilteritinib-arm patients with R/R *FLT3*$^{mut+}$ AML living without relapse underwent HSCT followed by gilteritinib maintenance. Pre-HSCT remission rates and post-HSCT survival were similar across arms. Post-HSCT gilteritinib maintenance may relate to the low post-HSCT relapse rate in gilteritinib-treated patients. Gilteritinib's safety appears stable at 2 years.

09.19

Effect of pembrolizumab monotherapy versus brentuximab vedotin on symptoms associated with health-related quality of life (HRQoL) in relapsed/refractory classical Hodgkin lymphoma (R/R cHL) in the randomized phase 3 KEYNOTE-204 study

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Aim: To evaluate patient-reported outcomes (PROs), based on the EORTC QLQ-C30 scale, and the effects of pembrolizumab and brentuximab vedotin (BV) on the presence and resolution of B symptoms and HRQoL among patients with R/R cHL in the phase 3 KEYNOTE-204 study (NCT02684292).

Method: BV-naive/BV-exposed patients (≥18 years) who had measurable disease with ECOG PS 0/1 and R/R cHL after autologous stem cell transplant (ASCT), or who were ASCT ineligible, were included. Patients were randomly assigned 1:1 to pembrolizumab 200 mg IV Q3W (n=151) or BV 1.8 mg/kg IV Q3W (n=153). End points for analysis of PROs were EORTC QLQ-C30 symptom scores (fatigue, pain, nausea/vomiting) from baseline to week 24 and presence and resolution of B symptoms.

Results: 296 patients were included in the PRO analysis (pembrolizumab, 146; BV, 150) LSM change in EORTC QLQ-C30 was lower (ie, better functioning) with pembrolizumab than BV for fatigue (LSM difference, –11.88; 95% CI, –17.26, –6.50; two-sided nominal $P<0.0001$) and pain (–6.03; –11.70, –0.36; two-sided nominal $P=0.0371$) scores; no treatment differences were observed for the nausea/vomiting symptom score. Of 300 patients treated, 78 (pembrolizumab, n=42; BV, n=36) experienced B symptoms at baseline, whereas 40 (pembrolizumab [95.2%]) and 27 (BV [75.0%]) experienced resolution of B symptoms during the study (RR, 1.27 [95% CI, 1.05-1.52]; two-sided $P=0.013$). Of 222 patients who did not experience B symptoms at baseline, 10/106 (pembrolizumab [9.4%]) and 14/116 (BV [12.1%]) experienced B symptoms during treatment. Median time to first B symptoms was not reached in either group (HR, 0.44 [95% CI, 0.18-1.04]; two-sided $P=0.062$).

Conclusion: Pembrolizumab improved HRQoL versus BV at week 24. B symptoms were more likely to resolve in pembrolizumab-treated than BV-treated patients. Findings support pembrolizumab as the preferred treatment option for patients with R/R cHL who are ineligible for, or fail, ASCT.

09.20

Patient Characteristics of Long-term Responders to Mogamulizumab (Anti-CCR4 mAb): Results from the MAVORIC Study

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Aim: The MAVORIC phase 3, multi-center, randomised trial compared safety and efficacy of mogamulizumab with vorinostat in patients with mycosis fungoides or Sézary syndrome (SS) after ≥1 prior systemic therapy. For mogamulizumab-treated patients, global overall response rate (ORR; partial [PR] or complete response [CR]) was 28%(52/186); median duration of response (DOR) 14.1 months. This analysis assessed characteristics of patients with ORRs of different durations following treatment with mogamulizumab.

Methods: This *post hoc* analysis assessed 4 cohorts based on minimum DOR (≥4, ≥6, ≥8, and ≥12 months; ORR4, 6, 8, and 12). Linear regression and multivariate analysis (odds ratios [ORs] for ORR12 response) was performed for gender, performance status, disease type, stage(IB-IV), blood involvement, CCR4 expression, age, time from diagnosis, mSWAT and LDH. Minimal residual disease assessment (MRD) samples for TCR analysis after blood CR were collected from two SS patients in the ORR12 cohort.

Results: RRs by disease compartment for patients treated ≥12 months are shown in Table1. For mogamulizumab (n=186), ORRs lasting ≥4, ≥6, ≥8, and ≥12 months were seen in 25.3%, 21.0%, 16.1%, and 10.8% respectively. Responses in blood and skin lasting ≥6 months were seen in 49.2% and 27.4% vs 5.6% and 7.5% of vorinostat-treated patients. Comparison of the ORR12 group with other mogamulizumab-treated patients demonstrated ORR12 patients were more likely to have SS (P=0.016, OR 0.29), stage IVA1 disease (P=0.0002, OR 11.13), and blood involvement (P=0.03, OR 0.19). Multivariate analyses confirmed SS as a significant predictor of long-term response. In 2 patients with CR in the ORR12 cohort, molecular MRD monitoring confirmed deep remissions in blood lasting ≥47 months and 63 months.

Conclusion: Long-term (≥12 months) responders in the MAVORIC trial were those with SS, stage IVA1 or blood involvement. MRD analyses indicate the ability of mogamulizumab to produce lasting and deep responses in some patients.

Table1. Confirmed Response in MAVORIC Patients Achieving ≥12 Months Response with Mogamulizumab

	ORR4		ORR6		ORR8		ORR12	
	Vori	Moga	Vori	Moga	Vori	Moga	Vori	Moga
Global ORR* (n, %)	8 (4.3) n=186	47 (25.3) n=186	6 (3.2) n=186	39 (21.0) n=186	4 (2.2) n=186	30 (16.1) n=186	0 n=186	20 (10.8) n=186
95% CI	(1.9, 8.3)	(19.2, 32.1)	(1.2, 6.9)	(15.4, 27.5)	(0.6, 5.4)	(11.2, 22.2)	-	(6.7, 16.1)
Blood response* (n, %)	10 (8.0) n=125	68 (54.8) n=124	7 (5.6) n=125	61 (49.2) n=124	4 (3.2) n=125	54 (43.5) n=124	3 (2.4) n=125	35 (28.2) n=124
95% CI	(3.9, 14.2)	(45.7, 63.8)	(2.3, 11.2)	(40.1, 58.3)	(0.9, 8.0)	(34.7, 52.7)	(0.5, 6.9)	(20.5, 37.0)
Skin response* (n, %)	18 (9.7) n=186	62 (33.3) n=186	14 (7.5) n=186	51 (27.4) n=186	14 (7.5) n=186	43 (23.1) n=186	9 (4.8) n=186	26 (14.0) n=186
95% CI	(5.8, 14.9)	(26.6, 40.6)	(4.2, 12.3)	(21.1, 34.4)	(4.2, 12.3)	(17.3, 29.8)	(2.2, 9.0)	(9.3, 19.8)
Nodal response* (n, %)	5 (3.8) n=133	19 (14.0) n=136	3 (2.3) n=133	16 (11.8) n=136	2 (1.5) n=133	8 (5.9) n=136	1 (0.8) n=133	3 (2.2) n=136
95% CI	(1.2, 8.6)	(8.6, 21.0)	(0.5, 6.5)	(6.9, 18.4)	(0.2, 5.3)	(2.6, 11.3)	(0.0, 4.1)	(0.5, 6.3)
Viscera response* (n, %)	0 n=4	0 n=6	0 n=4	0 n=6	0 n=4	0 n=6	0 n=4	0 n=6
95% CI	-	-	-	-	-	-	-	-

*Composite of all compartments, confirmed (CR+PR).
CI, confidence interval; Moga, mogamulizumab; ORR, overall response rate; Vori, vorinostat.

09.21

Safety and efficacy of zanubrutinib in patients with relapsed/refractory marginal zone lymphoma (MAGNOLIA Phase 2 Study)

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Aim: Zanubrutinib is a potent, next-generation BTK inhibitor with higher selectivity for BTK versus the TEC- and EGFR-family kinases. The initial efficacy and safety results of zanubrutinib in patients with relapsed/refractory marginal zone lymphoma (R/R MZL) enrolled in the MAGNOLIA study (BGB-3111-214; NCT03846427) are presented.

Methods: In this single-arm, multicenter study, adults with R/R MZL who previously received ≥1 prior therapy including ≥1 CD20 antibody regimen received zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) by independent review committee (IRC). Secondary endpoints included investigator-assessed ORR (ORR_{INV}), duration of response (DOR), progression-free survival (PFS), and safety.

Results: As of January 11, 2021, 68 patients were enrolled and treated. Median age was 70 years (range, 37-95), with 28% aged ≥75 years. In these patients, MZL subtypes included extranodal (38%), nodal (38%), splenic (18%), and indeterminate (6%). Median number of prior therapies was 2 (range, 1-6), and 32% of patients had disease refractory to last therapy.
Median duration of exposure was 59.1 weeks (range, 3.7-84.1). After a median follow-up of 15.5 months (range, 1.6-21.7), ORR_{INV} was 74% with a complete response rate of 24% (**Table**); responses were observed in all subtypes. Median DOR and PFS were not reached. IRC review is ongoing.
Twenty-eight (41%) patients discontinued treatment (n=20, disease progression; n=4, adverse events [AEs]). The most common treatment-emergent AEs reported in ≥10% of patients were diarrhoea (22%), bruising (21%), and constipation (15%); neutropenia was the most common grade ≥3 AE (10%). All-grade AEs of interest included neutropenia (13%), thrombocytopenia (13%), atrial fibrillation/flutter (3%), and hypertension (3%). No major/serious haemorrhage was reported. No AEs led to dose reductions.

Conclusion: Zanubrutinib demonstrated high response rates and durable disease control with a favourable safety profile in patients with R/R MZL.

Efficacy (investigator assessment)	**(N=66)[a]**
ORR, n (%) [95% CI]	49 (74%) [62, 84]
Complete response	16 (24%)
Partial response	33 (50%)
Stable disease[b]	11 (17%)
Progressive disease	5 (8%)
Discontinued study before first assessment	1 (2%)
Time to response in months, median (range)	2.8 (1.7, 8.5)
Safety	**(N=68)[c]**
Any AE, n (%)	65 (96%)
Grade ≥3 AE, n (%)	26 (38%)
Serious AE, n (%)	25 (37%)
AE leading to dose interruption, n (%)	19 (28%)

[a]Efficacy-evaluable set: patients who received at least one dose of study drug and with centrally-confirmed diagnosis of MZL (two patients were excluded due to MZL transformation to diffuse large B-cell lymphoma).
[b]Three patients with stable disease were continuing on study treatment.
[c]Safety analysis set: all patients who received at least one dose of study drug.

09.22

First Results of a Head-to-Head Trial of Acalabrutinib versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia (CLL)

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Aim: Increased selectivity of the Bruton tyrosine kinase inhibitor (BTKi) acalabrutinib (Aca) vs ibrutinib (Ib) may improve tolerability. We conducted an open-label, randomized, noninferiority, phase-3 trial to compare Aca vs Ib in patients (pts) with CLL.

Method: Pts with previously treated CLL and del(17p) or del(11q) were randomized to receive oral Aca 100mg BID or Ib 420mg QD until disease progression or unacceptable toxicity. Primary endpoint was progression-free survival (PFS) assessed by IRC; secondary endpoints of all grade atrial fibrillation (AF), grade ≥3 infection, rate of Richter transformation, and overall survival (OS) were assessed in hierarchical order.

Results: 533 pts (Aca, n=268; Ib, n=265) were randomized (median age 66 y; median 2 prior therapies; del(17p) 45.2%; del(11q) 64.2%). At a median follow-up of 40.9 mo (range 0.0–59.1), Aca was noninferior to Ib with a median PFS of 38.4 mo in both arms (HR 1.00; 95% CI 0.79–1.27). Aca was statistically superior to Ib in all-grade AF incidence (9.4% vs 16.0%; P=0.023). Rates of grade ≥3 infection (Aca: 30.8%, Ib: 30.0%) and Richter transformation (Aca: 3.8%, Ib: 4.9%) were comparable between arms. Median OS was not reached in either arm (HR 0.82 [95% CI 0.59–1.15]), with 63 (23.5%) deaths in the Aca arm and 73 (27.5%) in the Ib arm. Aca was associated with a lower incidence of any grade hypertension (9.4%, 23.2%), arthralgia (15.8%, 22.8%), and diarrhea (34.6%, 46.0%) but a higher incidence of headache (34.6%, 20.2%) and cough (28.9%, 21.3%). AEs led to treatment discontinuation in 14.7% of Aca- vs 21.3% of Ib-treated pts. Among any-grade events of clinical interest, cardiac, hypertension, and bleeding events were less frequent with Aca.

Conclusion: In this first comparative trial of BTKis in CLL, Aca demonstrated non-inferior PFS with less cardiotoxicity and fewer discontinuations due to AEs vs Ib.

09.23

Patterns of treatment and outcomes in patients with large B-cell lymphoma: The Australian real-world experience

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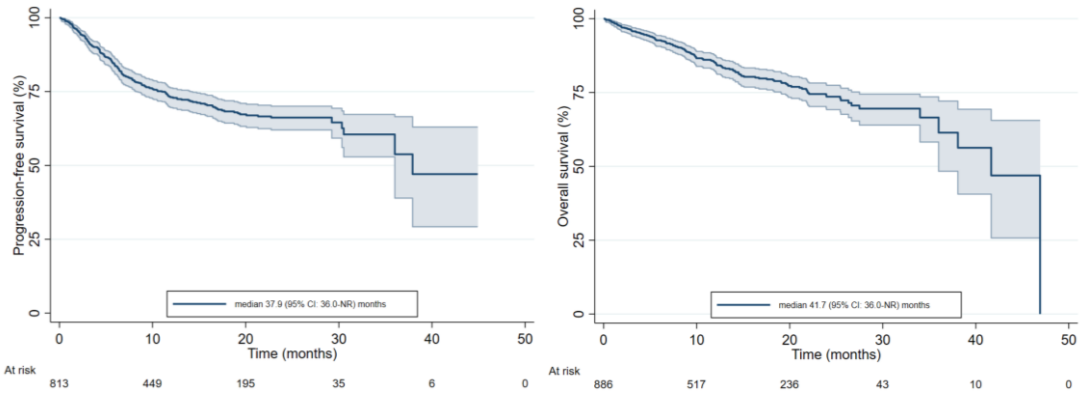
Aim: Data are limited regarding treatment patterns and outcomes for patients with diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL) in Australia. The objective was to describe treatment selection and outcome of patients within the Lymphoma and Related Diseases Registry (LaRDR) and identify areas of need for this patient group.

Method: LaRDR is a prospective registry operating at 26 sites since 2016. Baseline characteristics and treatment data were tabulated, and comparisons between groups made with chi-squared tests. PFS and OS were reported using KM survival analysis with 95%CI.

Results: 928pts with newly diagnosed DLBCL (including DLBCL-DH/TH) and 43 with PMBCL registered in LaRDR from January 2016 to November 2020 were included. At diagnosis, median age was 67.7y and 30.2y with advanced stage in 61.4% and 16.3% in DLBCL and PMBCL, respectively. 51.8% DLBCL pts had GCB-type and 34.6% non-GCB-type COO. R-CHOP21 was the commonest 1L, however 40.0% (8/20) pts with DLBCL-DH/TH and 47.2% (17/36) PMBCL received intensified regimens. 8.1% (3/37) PMBCL pts received radiotherapy. 23.5% (51/217) elderly pts (age ≥75y) were given attenuated regimens. DLBCL (including DLBCL-DH/TH) CR rate was 72.8% whilst 30m PFS and OS were 66% and 71%, respectively (Figure below). Despite similar ORR, those ≥75y had inferior 30m PFS and OS of 52% and 53%, respectively. 164pts relapsed (142 “early”, i.e. within 12m) and received subsequent therapy, including ASCT (4.4%). 4.2%pts were enrolled into trials upfront, 2.3% at first and 33.3% at second relapse. DLBCL-DH/TH and IPI predicted early progression. 75.0% PMBCL pts achieved CR after 1L, with 30m PFS and OS of 87% and 92%, respectively.

Conclusion: Outcomes in Australia with DLBCL and PMBCL are comparable to registries in the USA and Europe. Variation in practice is present, especially in DLBCL-DH/TH and PMBCL. Trial utilisation is low in 1L and at first relapse.



09.24

Detection of cytogenetic abnormalities in Chronic Lymphocytic Leukaemia by imaging flow cytometry.

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Aim: Chromosomal abnormalities are detectable in up to 80% of patients with chronic lymphocytic leukaemia (CLL). Of these, the most significant is del(17p) seen in up to 8% of cases, and +12 occurs in 10-20%. Testing is by fluorescence *in situ* hybridisation (FISH) with an abnormality in 5-7% of nuclei regarded as positive. We explored the utility of a cutting-edge automated imaging flow cytometry method that incorporates cell phenotyping and FISH ("immune-flowFISH) to detect these abnormalities in CLL.

Method: Blood from 75 patients with CLL, at diagnosis or on therapy, were studied. After red cell lysis, samples were incubated with CD3, CD5 and CD19 fluorophore-conjugated antibodies. Following fixation and membrane permeabilisation, DNA was denatured and FISH probes to 17p12 and centromeres of chromosomes 12 and 17 were added. After 24 hours hybridisation, nuclei were stained and up to 200,000 cells acquired on the AMNIS ImageStreamX MkII. IDEAS software was used to assess the number and percent CD19/CD5-positive CLL cells with FISH abnormalities.

Results: A chromosomal abnormality was detected in 23/75 cases. Of these, 10 cases had only one 17p signal (but 2 for centromere 17), indicative of del(17p) in 2-35% of CD5/CD19-positive cells (i.e. 0.4-22% or 270-35,441 of all cells). In 13 cases, there were 3 FISH signals for CEP12, consistent with +12 in 0.1-46.0% of CLL cells (26-9,111 cells). The CD3/CD5-positive T cells had diploid signals for each probe in all cells. This data was evident on numerical analysis and on digital imagery.

Conclusion: Immuno-flowFISH could detect del(17p) and +12 in immunophenotyped CLL cells to a lowest level of 0.4% and 0.1% of all cells, respectively. Since this method analyses many thousand cells, and can assess FISH signals in phenotyped cells of interest, it adds a new dimension to chromosomal analysis in CLL, both at diagnosis and for monitoring

09.25

Anti-Tmprss6 RNAi therapy as a novel treatment option for Polycythaemia Vera

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Aim: Polycythaemia Vera (PV) is a rare blood cancer, where overproduction of red cells renders patients at increased risk of life-threatening thrombotic events. First line therapy, venesection reduces haematocrit and suppresses further red cell production, thus reducing thrombosis risk. However, associated systemic iron deficiency and fluid shifts cause side effects that can severely impair quality of life.

Hepcidin, the master regulator of systemic iron homeostasis, is normally suppressed in iron deficiency or by increased erythropoiesis. Interestingly, hepcidin levels are not suppressed in PV, suggesting relative upregulation. We hypothesised that further upregulation of hepcidin in PV would improve disease severity. We aimed to discover whether therapeutically increasing endogenous hepcidin expression in PV through knock-down of its regulator, *Tmprss6*, could act as a medical venesection.

Method: We developed an inducible, bone marrow transplant PV mouse model. Mice were administered anti-*Tmprss6* or non-targeting control siRNA once every 3 weeks for 3 doses, before organs were collected for downstream analysis.

Results: Untreated PV mice had comparable levels of hepcidin as control mice. PV mice administered anti-*Tmprss6* siRNA had increased hepcidin levels, which significantly decreased serum iron but did not cause iron deficiency in peripheral organs. PV animals administered anti-*Tmprss6* siRNA had significantly lower haematocrit (45.9 vs 61.2%; P<0.0001), haemoglobin levels (12.0 vs 17.7g/dL; P<0.0001) and mean cell volume (36.1 vs 48.4fL, P<0.0001) than those treated with control siRNA.

Conclusion: These data provide pre-clinical evidence that increasing endogenous hepcidin could be a viable therapeutic avenue for PV treatment. This treatment approach does not affect fluid levels and may reduce risk of systemic iron deficiency, the two concerns with venesection. A related siRNA compound targeting *TMPRSS6,* SLN124, is in clinical development for hepcidin deficient anaemias. SLN124's long-lasting duration of action coupled with patient friendly administration route could provide benefit by decreasing venesection requirement and increasing comfort for PV patients.

09.26

Incorporation of genomic features in the prognostic assessment of myelodysplastic syndromes (MDS): a 5-year experience at Royal Melbourne Hospital and Peter MacCallum Cancer Centre.

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Aim:

1. To establish the clinical outcomes of MDS at Royal Melbourne Hospital and Peter MacCallum Cancer Centre between 2016 and 2020.
2. To assess if the predictive values of IPSS-R in MDS can be enhanced by incorporating genomic features using two published models: MIPSS-R[1] and molecular IPSS-R[2].

Method: A retrospective review of medical records of all newly diagnosed MDS at Royal Melbourne Hospital and Peter MacCallum Cancer Centre was conducted between August 2016 and December 2020 including demographic, disease and treatment information.

Results: Fifty-seven patients were identified, 39 (68%) de-novo MDS and 18 (32%) therapy-related MDS (t-MDS). Median age of de-novo and t-MDS cohort was 75 years (range, 45-90) and 68 years (range, 36-80), respectively. Forty-nine patients (86%) had disease-specific genomic information. Median follow-up was 18 months (range, 3.8-45.1 months). Fifteen (26.3%) of all MDS patients were treated (13 azacitidine, 1 lenalidomide, 1 erythroid stimulating agent).

IPSS-R was predictive of survival outcomes in both MDS and t-MDS cohorts (Table, Figure 1). Application of mutational scores based on number of mutations in the MIPSS-R model, did not improve prognostication of de-novo MDS and t-MDS (Figure 2). In contrast, the molecular IPSS-R model which incorporates specific mutations that impact OS (SF3B1, EZH2 and TP53) performed better than MIPSS-R at predicting the prognosis of de-novo MDS and t-MDS cohorts.

Prognostic model and prediction of OS	*Very Low/ Low risk (months)*	*Intermediate risk (months)*		*High/ Very High risk (months)*	*p value*
IPSS-R					
MDS	36.2	19.3		18.9	0.07
t-MDS	45.1	25.4		8.6	0.009*
MIPSS-R					
MDS	Not reached	18.9		32.0	0.12
Molecular IPSS-R					
MDS	Not reached	(Int-1) 38.0	(Int-2) 36.2	15.1	0.07
t-MDS	43.5	N/A	21.3	8.6	-

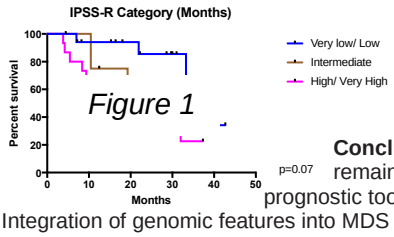

Figure 1

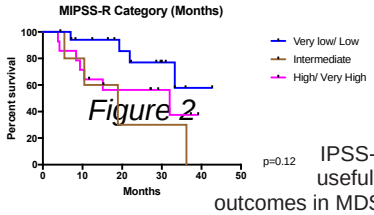

Figure 2

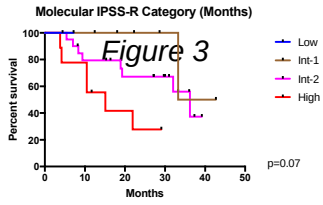

Figure 3

Conclusion: IPSS-R remains a useful prognostic tool in clinical outcomes in MDS. Integration of genomic features into MDS prognostication can refine ability to predict prognosis.

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09.27

High frequency of pathogenic germline variants in older adults with myeloid neoplasms

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Background: Germline predisposition is increasingly being recognised in myeloid neoplasms (MN) including primary myelodysplastic syndrome. Although majority of MN patients are older, research in germline predisposition is focussed on children and young adults. An unequivocal understanding of germline predisposition may inform surveillance (i.e. genetic counselling), risk stratification and prevention (i.e. donor selection) of MDS.

Aim: This study assesses frequency and type of pathogenic germline variants in MDS patients and compares with age matched healthy controls and patients with other cancers.

Method: We analysed 68 known cancer predisposition genes in germline samples of 142 samples from myeloid neoplasms. Study included primary MDS (n=51) and MDS diagnosed in cancer survivors with or without prior exposure to cytotoxic therapy (n=91). Using uniform American College of Medical Genetics and Genomics (ACMG) guidelines for annotating germline mutation, we also compared the frequency of pathogenic germline variants in the same genes with patients with single cancer and age-match healthy controls (>70 years).

Results: Pathogenic germline variants (PGVs) were identified in 14% (20/142) patients compared to 4% and 3% patients with single cancer and age-matched controls respectively (*P*<0.0001). Median age at diagnosis was similar between MN patients with or without PGVs [66 years (19-81) vs. 70 years (33-87); *P*=0.06]. PGVs were most frequent in *DDX41* (n=7, 33%) followed by *BRCA1* (n=2, 10%), *GATA2* (n=2; 10%) and *TP53* (n=2; 10%). The distribution of PGVs was also different, with *DDX41* PGVs absent in single cancers and more prevalent in MN than age-matched controls (35% vs. 4%, *P*<0.001). The frequency of PGV was 20%, 16%, 10% and 6% in patients ≤60, 61-70, 71-80 and >80 years of age (**Fig. 1**).

Conclusion: The frequency of PGVs is significantly high in MN compared to age matched healthy control and other cancer patients. This provides evidence for genetic predisposition testing in MN patients.

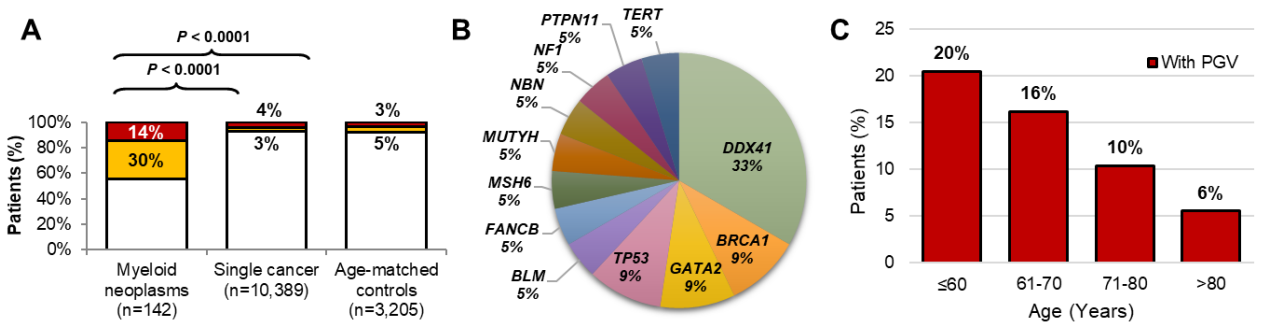

Fig. 1 Pathogenic germline variants (PGVs) are frequent in cancer predisposing genes and have different distribution pattern compared to patients with single cancer and age-matched controls.

09.28

Therapy-related myeloid neoplasm has a distinct bone marrow microenvironment, probably induced by prior cytotoxic therapy

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Background: Therapy-related myeloid neoplasms (t-MN) are associated with dismal outcomes in otherwise long-term cancer survivors and are considered to be a direct consequence of DNA damage induced in haematopoietic stem cells (HSC) by cytotoxic therapy (CT). However, it largely ignores CT induced changes to bone marrow (BM)-microenvironment.

Aims: (i) to compare BM-microenvironment in t-MN with that of other-MN and age-matched healthy control, (ii) to decipher CT-induced changes from that of MN induced changes in BM-microenvironment. BM-mesenchymal stromal cells (MSC) phenotype, function, and whole transcriptome was compared in four well selected cohorts of: (1) t-MN, in which MN occurred in cancer survivor following exposure to CT; (2) MN developing in cancer survivors **without** prior exposure to CT; (3) MN without preceding independent cancer and/or exposure to CT and (4) age-matched controls (HC).

Results: t-MN-MSC exhibited aberrant morphology, impaired proliferation, DNA damage repair, differentiation capacity and increased senescence compared to age-matched HC and other-MN. t-MN-MSC also display Senescence Associated Secretory Phenotype and high expression of C*DKN1A*, a critical cyclin dependent kinase inhibitor orchestrating cell cycle arrest. Aberrant t-MN-MSC were unable to support haematopoiesis. Transcriptome analysis showed reduced expression of genes involved in DNA damage repair, cell cycle regulation and HSC-support pathways (Fig.1A).

Unlike other-MN, t-MN provides a unique opportunity to decipher the effect of aberrant BM-microenvironment in disease pathogenesis from that of malignant clone-induced changes in BM-microenvironment. Analysis of sequential BM samples elucidated aberrant BM-MSC proliferation and differentiation following CT, well before diagnosis of t-MN (Fig.1B).

Conclusion: This is the first comprehensive study demonstrating significant aberrant phenotype and poor HSC-supporting capacity and provides molecular insight for aberrant t-MN BM-microenvironment compared to age-matched HC and other-MN. Moreover, our findings suggest that CT-induces long-term irreversible damage to BM-microenvironment which impairs HSC-supportive capacity and potentially contributes to t-MN pathogenesis.

Fig. 1A Differential gene expression

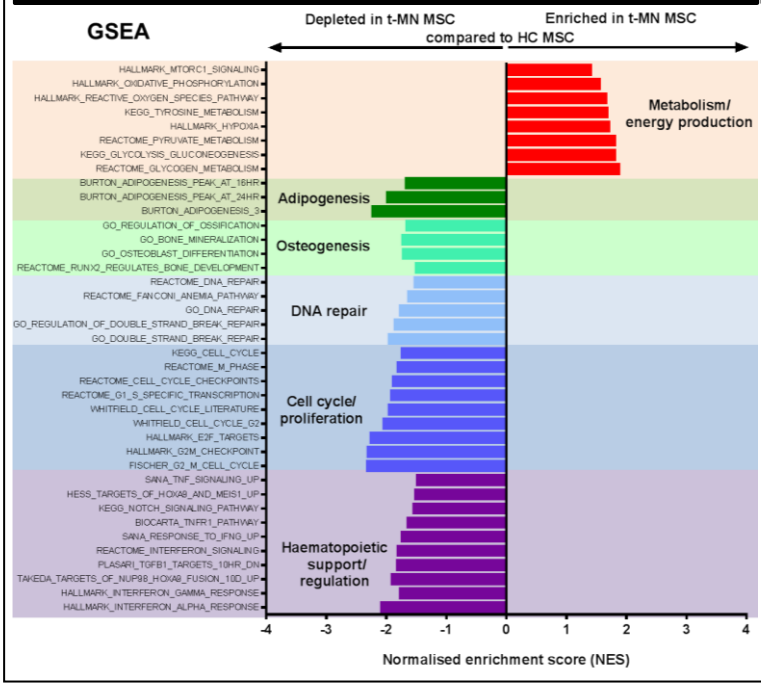
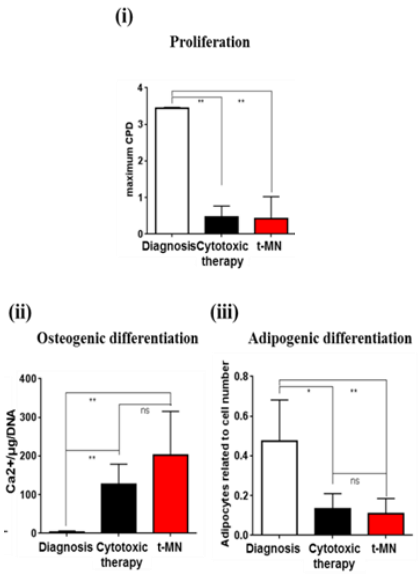


Fig. 1B Long-term irreversible damage to BM microenvironment induced by CT



09.29

Platelets in myelofibrosis have increased expression of the pro-inflammatory cytokine GRO-α

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Aim: The underlying pathophysiology leading to fibrosis in myeloproliferative neoplasms is poorly understood. An immune process driving fibroblastic activity is thought to contribute to this process. GRO-α is an inflammatory chemoattractant cytokine with inducible expression in a variety of immune cells and in platelet granules. We sought to compare GRO-α expression in platelet mRNA in myeloproliferative neoplasms and specifically determine whether the levels were increased in patients with myelofibrosis.

Method: Platelets were isolated from EDTA-anticoagulated blood from 70 patients with myeloproliferative neoplasms (21 with polycythemia vera (PV), 33 essential thrombocythemia (ET), 16 myelofibrosis) and 15 controls. Platelet gene expression for *CXCL1* (GRO-α) was analysed using transcriptomic next-generation sequencing with the Ion AmpliSeq Transcriptome Human Gene Expression Kit. Torrent Suit Software v5.4 and DESeq2 were used to generate counts and perform differential gene expression analyses. Gene expression data was correlated with clinical diagnosis and bone marrow pathology, including reticulin content.

Results: *CXCL1* (GRO-α) transcript levels in PV and ET were comparable at 0.944-fold differential (padj=0.639). However, both PV and ET were lower than controls with 0.727-fold (padj=0.637) and 0.614-fold (padj=0.353) *CXCL1* (GRO-α) expression, respectively. For patients with myelofibrosis, *CXCL1* (GRO-α) transcript levels were 5.81-fold (padj=5.77×10^{-5}) greater than controls. In addition, they were 8.00-fold (padj=2.75×10^{-7}) and 9.46-fold (padj=4.11×10^{-10}) higher than in PV and ET respectively.

Conclusion: This platelet transcript data shows that platelets in myelofibrosis, but not ET or PV, have statistically significantly elevated *CXCL1* (GRO-α) expression. This support our hypothesis that pro-inflammatory mediators are involved in the pathogenesis of fibrosis in myeloproliferative neoplasms. GRO-α, which is produced by megakaryocytes and platelets and stored, is secreted from platelet granules upon activation and may drive the fibroblastic proliferation.

09.30

Characterisation of patients with low JAK2 V617F allelic burden

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Aim: *JAK2* V617F variant allele fraction (VAF) is linked to clinical phenotype and outcomes in myeloproliferative neoplasms (MPNs), but the clinical significance of a low VAF is uncertain. We aimed to characterise patients with low *JAK2* V617F allelic burden.

Method: We retrospectively reviewed 148 patients who underwent *JAK2* V617F analysis using digital droplet polymerase chain reaction at our institution between December 2019 and April 2021. In patients with VAF □10%, data on clinical and laboratory parameters as well as recorded diagnosis was collected. Patients with MPNs in blast phase were excluded.

Results: Of the 14/148 (9%) patients with VAF □10%, 57% were male and median age was 56 years. 7/14 patients were evaluated for thrombocytosis, 5/14 for erythrocytosis, and 2/14 for other causes.

Of the 7/148 (5%) patients with VAF □1%, 86% were male and median age was 58 years. 4/7 patients were evaluated for erythrocytosis, 2/7 for thrombocytosis, and 1/7 for eosinophilia. 1/7 patients had splenomegaly and none had a history of thrombosis. Median haemoglobin was 167g/L with haematocrit of 0.51, white cell count was $9.3x10^9$/L and platelet count was $228x10^9$/L. 3/4 patients with erythrocytosis had EPO levels measured, and all were normal. 6/6 patients with erythrocytosis or thrombocytosis had repeat *JAK2* testing; VAF slightly increased in 2 patients and decreased in 2 patients (VAF remained □1% in all), whilst *JAK2* V617F was not detected in 2 patients on repeat testing. Only 1/7 patients with VAF □1% was diagnosed with MPN (essential thrombocythaemia with thrombocytosis, splenomegaly, persistent *JAK2* V617F mutation with VAF 0.160%, and supportive bone marrow histology; of note myeloid NGS detected CALR and ASXL1 mutations).

Conclusion: *JAK2* V617F VAF □1% needs to be interpreted with particular caution, particularly in cases of erythrocytosis. Correlation with clinical and laboratory parameters including serum EPO is required, and repeat *JAK2* testing may be of value.

09.31

Updated results of ciltacabtagene autoleucel (cilta-cel), a B-cell maturation antigen (BCMA)–directed chimeric antigen receptor T-cell (CAR-T) therapy, in relapsed/refractory multiple myeloma (RRMM)

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Aim: Evaluate the safety and efficacy of cilta-cel in patients with RRMM.

Method: Patients had measurable disease, ≥3 prior regimens (or double refractory to PI and IMiD), and received anti-CD38. After cyclophosphamide/fludarabine lymphodepletion, a targeted dose of 0.75×10^6 ($0.5–1.0\times10^6$) CAR+ viable T cells/kg was infused. Primary objectives were to assess safety and confirm the recommended phase 2 dose of cilta-cel (phase 1b) and to evaluate efficacy (phase 2). Response was assessed per IMWG criteria. CRS was graded by Lee 2014 and neurotoxicity by CTCAE in phase 1b; both were graded by ASTCT criteria in phase 2. Here, Lee 2014 and CTCAE grading were mapped to ASTCT criteria for CRS and ICANS, respectively.

Results: At 12.4-month median follow-up, 97 patients (median of 6 prior lines) received cilta-cel. ORR was 97% (95% CI, 91–99), with 67% sCR. Median time to first response was 1 month (range, 1–9), and median time to ≥CR was 2 months (range, 1–15). Median duration of response was not reached. Of 57 MRD-evaluable patients, 93% were MRD-negative at 10^{-5}. The 12-month PFS and OS rates (95% CI) were 77% (66–84) and 89% (80–94), respectively; median PFS was not reached. Grade 3/4 hematologic AEs included neutropenia (95%), anemia (68%), leukopenia (61%), thrombocytopenia (60%), and lymphopenia (50%). CRS occurred in 95% of patients (4% grade 3/4); median time to onset was 7 days (range, 1–12). CAR T-cell neurotoxicity occurred in 21% of patients (10% grade ≥3). Fourteen deaths occurred during the study: none ≤30 days, 2 ≤100 days, and 12 >100 days post-infusion, of which 5 were due to disease progression and 4 due to treatment-related AEs.

Conclusion: A single cilta-cel dose yielded early, deep, and durable responses in heavily pretreated patients with RRMM, with a manageable safety profile at the RP2D.

09.32

Reduction in absolute iFLC and dFLC is associated with prolonged major organ deterioration progression-free survival in newly diagnosed AL amyloidosis patients receiving VCd with or without daratumumab: results from ANDROMEDA

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Aim: Daratumumab plus bortezomib, cyclophosphamide, and dexamethasone (VCd) significantly improves outcomes in patients with systemic light-chain (AL) amyloidosis. ANDROMEDA (NCT03201965) assessed the impact of achieving reduced absolute involved free light-chain (iFLC) and the difference (dFLC) between iFLC and uninvolved FLC on major organ deterioration progression-free survival (MOD-PFS) as a key secondary endpoint.

Method: Patients with newly diagnosed AL amyloidosis with ≥1 involved organ, cardiac stage I-IIIA, eGFR ≥20 mL/min, and absent symptomatic multiple myeloma were randomly assigned (1:1) to receive daratumumab+VCd or VCd. Patients received subcutaneous bortezomib, oral/intravenous cyclophosphamide, and oral/intravenous dexamethasone for six 28-day cycles. Subcutaneous daratumumab was administered once weekly (Q1W; Cycles 1-2), Q2W (Cycles 3-6), and Q4W thereafter for up to 24 cycles. Disease evaluations occurred Q4W (Cycles 1-6) and Q8W thereafter, until major organ deterioration, death, study completion, or withdrawal. Primary endpoint: overall hematologic complete response (CR). Deep hematological response criteria: iFLC ≤20 mg/L and dFLC <10 (regardless of FLC ratio). MOD-PFS was defined as death; cardiac deterioration requiring transplant/left ventricular assist device/intra-aortic balloon pump; end-stage renal disease requiring hemodialysis/transplant; or hematologic progression.

Results: Overall, 388 patients (median age, 64 years) received daratumumab+VCd (n=195) or VCd (n=193). Between-group baseline characteristics were balanced. Involvement of ≥2 organs occurred in 65%: heart (71%), and kidney (59%); 23%, 40%, and 37% had cardiac stage I, II, and IIIA, respectively. Median treatment duration was 9.6 (daratumumab+VCd) and 5.3 months (VCd). Median follow up was 11.4 months. Daratumumab+VCd vs VCd had strongly favorable rates of deep hematological responses by all criteria (hematologic CR, 53% vs 18%; iFLC, 71% vs 20%; dFLC, 64% vs 31%) and longer MOD-PFS; the MOD-PFS was similar across all hematological response criteria.

Conclusion: Daratumumab+VCd increased deep hematologic response rates and prolonged MOD-PFS in patients with newly diagnosed AL amyloidosis.

09.33

Whole genome sequencing identifies drivers of extra medullary progression in multiple myeloma

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Title: Whole genome sequencing identifies drivers of extramedullary progression in multiple myeloma.

Aim: In patients with multiple myeloma, the development of extramedullary (EM) plasmacytomas (EP) correlates with chemotherapy resistance and dismal prognosis[1]. We aimed to identify single nucleotide variation mutations (SNV) and copy number variations (CNV) that drive the development of EPs using whole genome sequencing (WGS).

Method: 7 patients with non-extraosseous EM were included in this pilot study. 3 had contemporaneous prospective biopsies of bone marrow (BM) and EPs. Germ-line (GL) DNA was collected using buccal swabs. Four previous patients with EM disease were identified from pathology records; two had historic contemporaneous BM and EM biopsies, 2 had only EM samples. DNA was obtained from formalin-fixed paraffin-embedded (FFPE) specimens, while GL DNA was collected either using buccal swabs, stored peripheral blood mononuclear cells or stored autologous stem cells. Library for WGS was prepared using the xGen PRISM™ kit (IDT™). WGS was performed at the Australian Genomic Research Facility. Data was analysed using the Broad Institute's GATK workflows for identifying somatic SNV and CNV. Biological pathways were identified from gene set enrichment analyses of frequently mutated genes (SNVs and CNVs).

Results: WGS data was generated for all 7 patients, despite poor quality DNA from FFPE samples. CNV analysis showed increased rates of amplification of 1q in EM samples and loss of chromosome 13. On average, 1500 SNVs and indels were identified in EM samples. In patients with both BM and EM samples, an average of 909 mutations were found in EM samples that were not identified in BM samples. These mutations frequently occurred in KEGG pathways surrounding adhesion and extracellular matrix.

Conclusion: Mutations in EM disease cluster in pathways involved in cellular adhesion and extracellular matrix, providing insight into potential mechanisms of progression to EM disease. Furthermore, CNV analysis identifies increased rates of high-risk features, including amp(1q) and del(13).

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09.34

A randomised study of daratumumab, bortezomib, cyclophosphamide and dexamethasone induction with daratumumab until progression (VCDD) versus VCD induction alone for the initial treatment of transplant-ineligible patients with multiple myeloma (AMaRC03-16)

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Aim: To determine if addition of daratumumab to VCD will improve outcomes in patients with newly diagnosed transplant ineligible multiple myeloma.

Method: Inclusion criteria included untreated patients with symptomatic myeloma who were considered ineligible for high-dose chemotherapy with autologous stem cell transplantation due to either age >65years or the presence of comorbidities. Any degree of renal impairment, including dialysis dependence, was allowed as were patients with a prior history of systemic malignancy that had been disease-free for 2 years. Patients were randomised 1:1 to receive weekly VCDD followed by daratumumab every 4 weeks until progression or weekly VCD alone. The primary endpoint was PFS with secondary endpoints being response rates, MRD, overall survival, toxicity and quality of life.

Results: 121 patients were randomised, 64 received VCDD and 58 received VCD. Baseline characteristics were balanced between the two arms. Median age was 76 years (range, 62-91yrs), with 19% being ≥80 years of age. 30% were female. ECOG performance status was ≥ 2 in 19%). ISS stage was I (19%), II (47%), III (27%).

Overall response rate was 93% for VCDD and 81% for VCD. There was no significant difference between response rates after 4 cycles of induction for the VCDD and VCD arms: CR 2% vs 2%, VGPR 43% vs 29%, PR 48% vs 50%, MR 7% vs 10%, SD 0% vs 7%, PD 0% vs 2%. After a median follow up of 18.7 months, median PFS for those treated with VCDD was 23.3 months (95% CI 19-NR) and was 18.9 months (95%CI 15.3-28.2) for those treated with VCD (p=0.157).

Conclusion: In this pre-planned interim analysis, daratumumab with VCD was deliverable in an elderly population with multiple comorbidities, with a numeric improvement in deep responses. Further follow-up will be required to assess the impact on survival outcomes and an updated analysis will be presented

09.35

Assessing the immune tumour microenvironment (iTME) using multiplex immunofluorescence histochemistry (mIHC) demonstrates close proximity of cytotoxic T-cells to plasma cells (PC) in patients with newly diagnosed multiple myeloma (NDMM)

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Aim: A dysfunctional iTME facilitates disease progression in MM. Studies have demonstrated the association between the spatial distribution of immune cells and progression of various cancers. Using mIHC we aim to describe quantitative and qualitative changes in CD3+CD8+ T-cells ($T_{cytotoxic}$) in patients with MGUS, ND and relapsed/refractory MM (RRMM) and assess spatial proximity to PCs.

Method: Formalin-fixed, paraffin-embedded trephine sections from pts with MGUS (n=32), NDMM (n=65) and RRMM (n=59) were sequentially stained for CD138, CD3, CD8 and checkpoint receptors (CPs) Tim3, Lag-3 and PD-1. Halo® image analysis platform was used for cell segmentation and phenotyping, facilitating enumeration of $T_{cytotoxic}$ populations and analysis of proximity to PCs. Descriptive statistics and ordinary one-way ANOVA were applied as appropriate.

Results: Patient demographics, disease characteristics, treatment (including prior therapies, where applicable), best response, duration of response, median progression free (PFS) and overall survival (OS) will be presented for all cohorts. There was no difference in BM cellularity or total number of nucleated cells assessed across the cohorts (p=0.16 and p=0.25). PC % was higher in the ND and RRMM compared to MUGS cohort (p<0.001). The average distance between $T_{cytotoxic}$ and PCs was similar between the cohorts (p=0.38), but a higher proportion of $T_{cytotoxic}$ were within 50µm of a PC in the ND cohort (p=0.0036, 90.8±15.8% (ND) vs. 77.6±19.5% (MGUS) and 80.1±25.9% (RR)). The % of unique PCs with a single $T_{cytotoxic}$ within 100µm is higher in patients with MGUS and RRMM than NDMM (p=0.0007). There was no difference in the %CD3+, %CD3+CD8+ or %CD3+ cells expressing CD8 (p=0.22, p=0.62, p=0.48). CP expression on $T_{cytotoxic}$ was similar (Tim3 p=0.46, Lag-3 p=0.35; PD-1 p=0.54) with no difference in dual or triple CP expression. Sub-analyses assessing CP expression patterns and $T_{cytotoxic}$/PC proximity within individual cohorts based on response to treatment/disease progression are to follow.

Conclusion: The infiltration of cytotoxic T cells into tumours is a critical factor in immunotherapy efficacy. Here we clearly demonstrate the feasibility of mIHC to describe the spatial context of the iTME and we plan to implement it for predictive value in future studies of immunotherapies in patients with MM.

09.36

Impact of biomarker (SLiM) inclusion to diagnostic criteria for myeloma: diagnosis with SLiM alone versus end organ damage (CRAB) in the ANZ Myeloma and Related Diseases Registry (MRDR)

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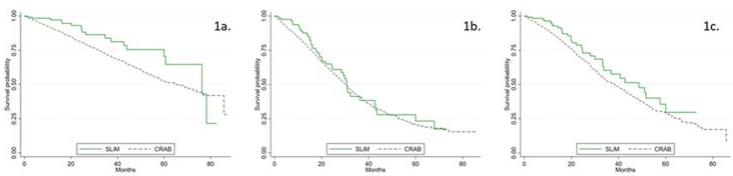
Aim: In addition to 4 CRAB diagnostic criteria, 3 biomarkers were adopted as myeloma-defining events to consensus international criteria in 2014: clonal bone marrow plasma cell (PC) percentage ≥60%, serum free light chain ratio (SFLCR) ≥100, and >1 MRI focal lesion, known as SLiM (SixtyLightchainMRI)[1]. Analysis of their clinical impact is needed.

Method: We compared characteristics, treatment and outcomes of 1686 patients diagnosed with CRAB and 132 with SLiM only criteria, enrolled in MRDR (2013-2018), to assess impact of these criteria on practice and outcomes.

Results: Of 132 SLiM patients, 48 had SFLCR≥100, 58 BMPC>60% and 26 had both (MRI lesions: insufficient data). More CRAB patients had advanced stage (R-ISS=3: 16.0 v 2.5%, p=0.001), poor performance status (ECOG 2-4: 24.7 v 8.3%, p<0.001) and FISH anomalies (66 v 55%, p=0.07), whereas SLiM had higher median PC% (60 v 50%, p=0.004) and SFLCR (100 v 39, p<0.001). Median OS of SLiM pts was longer than CRAB (76.3 v 65.2 m), p=0.02, HR 1.75 Fig 1a), with no difference in PFS (Fig 1b). However PFS2 was superior for SLiM: 48.7 v CRAB: 38.2 m (HR 1.38, p=0.06, Fig 1c). No difference in best response to treatment was seen in SLiM v CRAB. Within SLiM criteria, the proportion of patients per group with response <PR was, SFLCR: 3.6% (n=28), PC: 17.6% (n=34), Both: 20% (n=20); (p=0.04), indicating that patients who satisfy PC criteria (alone or with SFLCR>100) have higher risk for suboptimal response.

Conclusion: Superior OS in SLiM v CRAB with no difference in PFS1 could reflect earlier initiation of therapy in SLiM. However, the trend for longer PFS2 in SLiM indicates an improved outcome to first relapse therapy, suggesting shorter PFS2 of CRAB patients may result from more drug-resistant residual and re-emerging clones. These findings support initiating therapy by SLiM criteria.

Fig. 1(a) OS of pts diagnosed with active MM by SLiM vs CRAB criteria (76.3 vs 65.2 months, p=0.02, HR 1.75) (b) PFS of pts diagnosed with active MM by SLiM vs CRAB criteria (30.8 vs 30.2 months, p=0.3, HR 1.17) (c) PFS2 of pts diagnosed with active MM by SLiM vs CRAB criteria (48.6 vs 39.1 months, HR 1.38, p=0.06)



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09.37

RATIONAL: A randomised controlled feasibility trial comparing prophylactic immunoglobulin with oral antibiotics in patients with acquired hypogammaglobulinemia secondary to haematological malignancies

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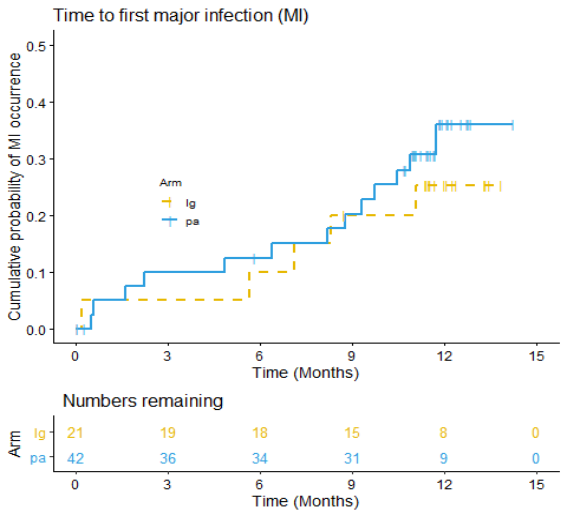
Aim: To determine the feasibility of delivering prophylactic oral antibiotics (PA) as an alternative to immunoglobulin (Ig) replacement in patients with haematological malignancies and acquired hypogammaglobulinemia.

Method: Phase II, multicentre, feasibility RCT (ACTRN12616001723471). Eligible patients had recurrent/severe bacterial infections or IgG level <4g/L and life expectancy > 12 months. Exclusion criteria included allogeneic stem cell transplant and Ig replacement in preceding 3 months. Patients were randomised to receive Ig (0.4g/kg IV every 4 weeks or 0.1g/kg/week SC) or daily PA (trimethoprim-sulfamethoxazole 160mg/800mg) for 12 months at a 1:2 ratio, stratified by site. Patients allocated to PA could crossover to Ig if they experienced a major (CTCAE ≥ Grade 3) infection. An independent, blinded outcome committee adjudicated infectious outcomes. Primary outcome was proportion of patients alive and on assigned treatment at 12 months. Secondary outcomes included time to first major infection.

Results: 63 patients were randomised. Median age was 69 years, 34 (54%) were female, 12 (19%) had myeloma, 29 (46%) chronic lymphocytic leukaemia, 20 (32%) non-Hodgkin lymphoma and 2 (3%) other malignancy. For the primary outcome, 76% (95% CI 53-92) in the Ig arm and 71% (95% CI 55-84) in the PA arm were alive and on assigned treatment at 12 months (p=0.77). Time to first major infection was similar between the two groups (figure 1, log rank test p=0.54). 74% of patients in Ig arm and 64% in PA arm were free of major infection during the 12 months.

Conclusion:
A similar proportion of patients allocated to Ig and PA remained alive and on assigned treatment at 12 months with no significant difference in time to first major infection. These findings support the feasibility of proceeding with a phase III trial to compare efficacy, safety and cost-effectiveness of PA to Ig replacement in patients with acquired hypogammaglobulinemia.



09.38

A comprehensive study of the incidence and geographic variation of haematologic malignancies diagnosed in North Queensland over a 10-year period

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Aim: To perform a detailed characterization of the incidence and geographical variation of haematologic malignancies in North Queensland using a clinically appropriate disease classification. Such high-quality epidemiological data will benefit numerous stake holders and allow for data-driven healthcare policies for blood cancer management.

Method: Retrospective, observational study of all adults diagnosed with a haematologic malignancy between 2005-2014 and residing within The Townsville Hospital Haematology catchment (data source: Queensland Cancer Registry). Comprehensive review of each patient's medical records was performed, updating each diagnosis to the 2017 WHO classification of tumours of haematopoietic and lymphoid tissues (e.g., 'malignant lymphoma' updated to specific histological subtype). Age-standardized incidence rates (ASRs) per 100,000 population, and incidence rate ratios (IRRs), were presented by geographic regions.

Results: 1581 haematologic malignancies (69%, lymphoid, 31% myeloid) were diagnosed, with 58 subtypes, and a rising number of new cases over the 10-years. The median age at diagnosis was 66-years, with a male predominance (60%). CLL was the most common lymphoid disorder, followed by plasma cell dyscrasias. MPNs were the commonest major subtype of myeloid disorders, followed by MDS and AML respectively. The ASR of haematologic malignancies ranged from 0.5-233.5/100,000 with large differences according to the geographical region. Postcode 4746, in the Mackay region, had the highest ASR (ASR=233.5). Similarly, the four highest IRRs were all within the Mackay region (postcodes 4739, 4746, 4750, 4799).

Conclusion: We successfully report, for the first time, the incidence of haematologic malignancies in North Queensland using a clinically meaningful disease classification. We advocate for such detailed characterization of the epidemiology of haematologic malignancies in wider Australia. The Mackay region is highlighted as a potential geographic hotspot. The reason for this is not clear from this study but possible explanations include the predilection for intensive, fertilizer-driven agriculture and mining in the region. Further investigation is warranted.

09.39

Multi-parameter flow cytometry demonstrates increased pro-inflammatory myeloid lineage in Transfusion dependent Beta Thalassaemia patients

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Title: Multi-parameter flow cytometry demonstrates increased pro-inflammatory myeloid lineage in Transfusion dependent Beta Thalassaemia patients
Aim: Despite the therapeutic advances in beta thalassaemia, cardiovascular disease remains a leading cause of mortality. The role of neutrophil subsets i.e. low density granulocytes (LDGs) and aged neutrophils, in the development of atherosclerosis and vascular inflammation, has recently been recognized [1]. The aim of this study was to study neutrophil and platelet inflammatory markers in transfusion dependent B thalassemia patients.
Method: We recruited 30 patients with beta thalassaemia major and 26 age and sex-matched healthy controls. Citrated blood samples were drawn before scheduled transfusion. LDG subset was determined as CD14lo/CD15hi/CD10hi whereas aged neutrophils as CD10pos/CD15pos/CD62Llo/CD182lo/CD184hi neutrophils [2]. Markers of neutrophil extracellular traps included citH3, MPO by flow cytometry and detection of dsDNA in plasma [3]. Analysis was by the BD LSRFortessa™ Flow Cytometer. Quantitative variables were compared using the Mann-Whitney test between patients of different groups. Data were analyzed using GraphPad, Prism software with a p value <0.05 considered as statistically significant.
Results: There were 18/13 males/females (mean age 32y) in the thalassemia group and 12/13 males/females (mean age 38 years) in the healthy group. Patients with beta thalassemia showed a significant increase in aged neutrophils (p<0.0001), LDGs (p<0.05) and CD40Lpos/CD62Ppos platelets (p<0.0001). Patients with beta thalassemia showed an increase in the NET marker plasma dsDNA (p<0.001).
Conclusion: Our results support an association of transfusion dependent thalassemia with an inflammatory profile of neutrophils and platelets which may contribute to the development of vascular damage. Targeting inflammatory neutrophil subsets may be a potential therapeutic avenue to prevent the development of cardiovascular disease in beta thalassemia major.

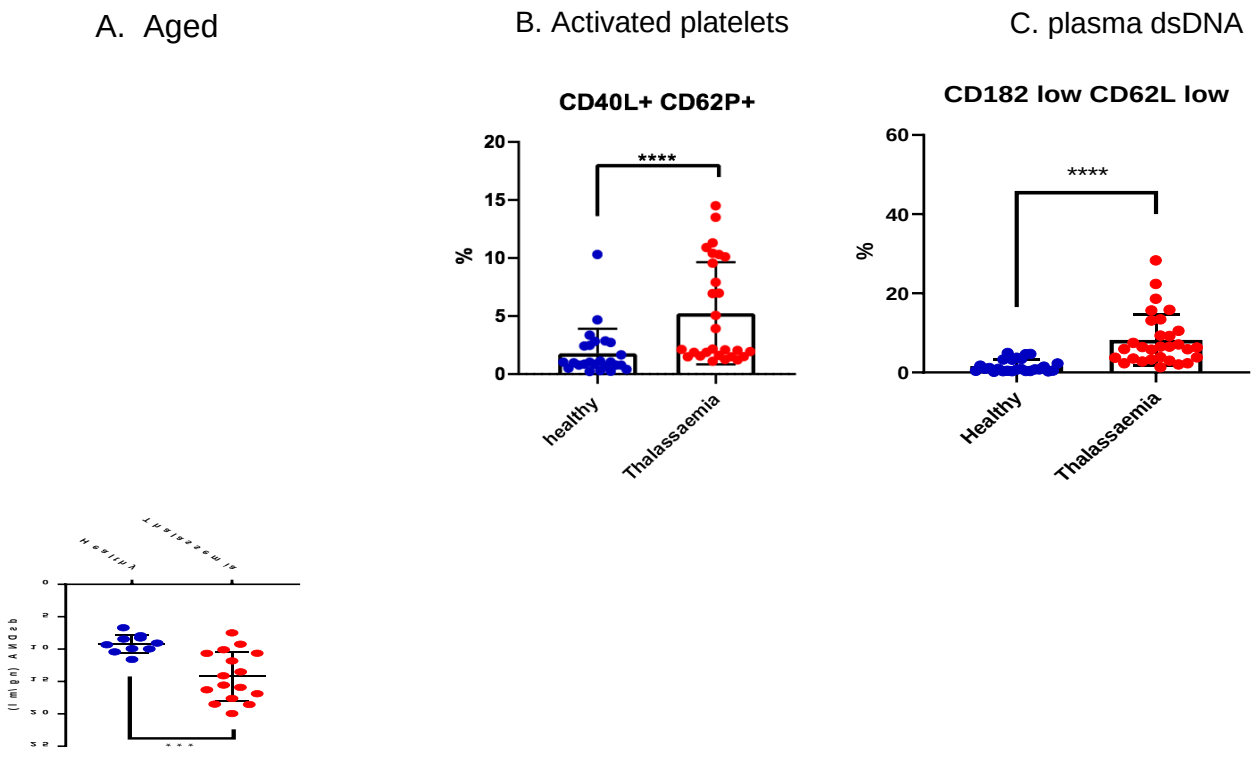

Figure. Thromboinflammatory markers in beta thalassemia major. A. Aged neutrophils (CD62LloCD182loCD184hi) as a percentage of total neutrophils (CD10posCD15pos) **B.** Activated platelets (CD40LposCD62Ppos) as a percentage of total platelets (CD42bpos) and **C.** Plasma levels of dsDNA in healthy individuals and patients with beta thalassemia major.

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1. *Teague…Mehta, JACC, Basic to translational science 2019*
2. *Perdomo…Chong, Nat Comm 2019*

09.40

Survival of patients with PNH treated with eculizumab in Australia compared with best supportive care: An analysis from the International PNH Registry

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Aim: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired haemolytic disorder that presents with multi-system manifestations related to chronic intravascular haemolysis and thrombosis caused by terminal complement activation that has historically resulted in poor survival. Eculizumab has been shown to improve survival though comparisons to outcomes achieved with best supportive care (BSC) are limited. Data from the International PNH Registry, an observational cohort study, was utilised to describe and compare overall survival of patients receiving BSC with Australian patients treated with eculizumab via the Life Saving Drugs Program (LSDP).

Methods: The study population consisted of 1) Australian patients treated with eculizumab (LSDP cohort), 2) all patients eligible to receive eculizumab (PNH granulocytes ≥10%, LDH ≥1.5 x ULN, and at least one other risk factor) at baseline (BSC cohort) enrolled in the Registry between August 2004 and January 2021. Survival probabilities and hazards ratios adjusted for sex, age, and history of bone marrow disorder (BMD) and/or thromboembolic event (TE) at baseline were generated using Cox proportional hazards modelling.

Results: Mean age of the LSDP cohort (N=68) was younger than the BSC cohort (N=230), 40.0 versus 48.3 years respectively at Registry enrolment. Females comprised 50% of the LSDP and 46% of the BSC population. History of BMD and TE in the LSDP cohort was 33% and 35% respectively compared to 66% and 12% in the BSC cohort. Eight-year survival for the LSDP cohort was 96.1% (95% CI 85.1, 99.0) vs the BSC cohort of 75% (95% CI 63.5, 83.3). Adjusted 8-year survival rates were 97% (91.7, 100.0) vs 82% (72.7, 92.4) for the LSDP and BSC cohorts, respectively corresponding to an 82% reduction in death (hazards ratio=0.18 (95% CI 0.04, 0.82) {p = 0.027}).

Conclusion: These data demonstrate that eculizumab, provided to Australian PNH patients under the LSDP, results in a significant improvement in survival.

Disclosures:
This study was supported by Alexion Pharmaceuticals, Inc.

09.41

Experiences and needs of people with haematological cancers during the COVID-19 pandemic: A qualitative study

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Aim: Haematological cancer patients are particularly vulnerable to the effects of COVID-19. In addition to being immunocompromised, pandemic-related travel restrictions have impacted access to treatments and overseas stem cell donations for haematological cancer patients requiring stem cell transplantation. Given this vulnerability, people with haematological cancers may experience heightened distress during the pandemic. This study aimed to explore haematological cancer patients' experiences, concerns, and unmet needs during this period of global uncertainty.

Method: Twenty-four Australian haematological cancer patients completed semi-structured interviews exploring their experiences during the pandemic, impact of pandemic on management of disease, perceived adequacy of information and support, lifestyle changes, and perceived benefits and challenges of using telehealth tools. Interview transcripts were thematically analysed.

Results: Four main themes reflecting the experiences of haematological cancer patients during the pandemic were identified: 'Sense of connection' (reduced social support and access to external support services); 'Fears about contracting COVID-19' (behaviour changes to protect health, impact on daily routine and habits, annoyance at dismissive attitude of others toward COVID-19); 'New challenges' (increased financial hardship, exacerbation of mental health issues and cancer-related symptoms), and; 'Underlying system and communication issues' (access to trusted information, satisfaction/dissatisfaction with care team, navigating telehealth). Participants expressed a need for improved access to support services and trusted information.

Conclusion: The findings emphasise the additional challenges experienced by haematological cancer patients during the COVID-19 pandemic and their impact on daily life. Results point to the importance of (i) validation of increased distress during periods of uncertainty; (ii) reinforcing recommendations about high-quality sources of information that address the specific impacts of COVID-19 for haematological cancer patients, especially those required to travel for treatment; and (iii) facilitating continued access to support services when face-to-face care is limited

09.42

Correlation of haemophagocytosis with clinical criteria of haemophagocytic lymphohistiocytosis and recommendations for screening bone marrow samples in adult patients.

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Introduction: Haemophagocytic lymphohistiocytosis (HLH) is a rare condition resulting from a dysregulated inflammatory response. It comprises of a constellation of clinical and laboratory criteria including haemophagocytosis. Currently there is lack of evidence on correlation between haemophagocytosis with the clinical diagnostic criteria for HLH, and no guidelines on the morphological identification of haemophagocytosis on bone marrow biopsy (BM).

Aim: We therefore aimed to assess if the amount of haemophagocytosis identified in the BM correlates with HLH-2004 criteria, and to formulate recommendations for morphological review of bone marrow specimens.

Method: A retrospective review of 62 bone marrow biopsies from 59 adult patients under investigation for HLH was undertaken independently by 2 haematopathologists who were blinded to the original biopsy report. The average number of actively haemophagocytic cells in each slide were quantified as 0, 1, 2-4 and ≥5. Discordant cases were reviewed by both assessors to reach consensus.

Results: An underlying haematological condition was identified in 34 cases out of 62 (58%). The most common underlying haematological condition was lymphoma (n=15, 25%). There was a significant association between the amount of haemophagocytosis and the number of HLH-2004 criteria met ($p<0.0001$). In patients where haemophagocytosis was present (n=31), there was a correlation between the amount of haemophagocytosis and ferritin ($p=0.041$). Our recommendations for the reporting of BM haemophagocytosis include assessing aspirate squashes and trails, as well as trephine biopsy, counting only intact haemopoietic cells within macrophages, counting cells away from particles, avoiding cell conglomerates and cells without clear margins, and use of CD68 immunohistochemistry.

Conclusion: Our findings indicate that the amount of haemophagocytosis present on BM samples correlates well with the number of HLH-2004 criteria. We also provide recommendations for morphological assessment of BM to reduce interobserver variability.

10. ANZSBT Free Communications

10.01

An update on wrong blood in tube (WBIT) events from the Serious Transfusion Incident Reporting (STIR) program.

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Background: WBIT events continue to occur and have the potential to result in an ABO incompatible transfusion. The STIR program has collected information on WBIT events since the inception of STIR (2006).

Aim: To describe events reported to STIR over time and assess for improvements.

Method: WBITs are reported as a separate near miss event including how and where they occur. Reporters complete de-identified information into a specific form. Data is reviewed, validated and collated for annual reports.

Results: From 2006 to 2014, 426 WBITs were reported (~53/year). In 2015, the reporting criteria changed to exclude specimens that had different patient details to the request as zero tolerance became more robust. From 2015-2020, 181 WBIT reports received (~36/year), with one report of an ABO incompatible transfusion. Failure of patient identity check remains the main contributor reported, followed by not labelling at the bedside, and incorrect use of pre-printed labels. Each year approximately 35-60% of WBIT occur in the emergency department or maternity.
Blood Matters has developed sample circle posters and ABCD of sample collection lanyards to help educate staff to correct process.
As health services move to electronic medical records (EMR), STIR will closely monitor changes in reporting patterns. Anecdotally, issues of EMR use leading to further WBITs have been described. It would be hoped that EMRs reduce the numbers. STIR investigation forms have been updated to capture potential issues related to electronic systems. Currently only a small number (8 since January 2021) of reports received where an EMR was used.

Conclusion: WBIT continues to occur and remains the largest proportion of procedural errors received by STIR. Clinical areas where patient identification may be more difficult remain areas of greatest concern. Monitoring of EMR implications in WBITs will continue, with data and any trends shared to help improve patient safety.

10.02

Who are the adult trauma injury patients with critical bleeding requiring massive transfusion? - a demographic profile analysis from the Australian and New Zealand Massive Transfusion Registry (ANZ-MTR)

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Aim: Describe the demographic profile of Australian and New Zealand patients (≥18-yrs) with critical bleeding due to trauma injury who received massive transfusion (MT) within 12h of hospital admission.

Method: Data were extracted from the ANZ-MTR for cases that satisfied the following criteria: 1) patient admitted to a hospital with Level 1 trauma facilities; 2) MT, defined as ≥5 red blood cell units within 4h, commenced within 12h of admission; 3) hospital records, including diagnostic coding data, were consistent with critical bleeding due to trauma injury. Extracted data included: patient sex, age, dates/times of admission/discharge, in-hospital mortality, diagnostic and procedure codes, transfusion and laboratory records. Injury mechanism and site(s) were categorised from diagnostic coding data. Patient age was stratified into categories (18-30, 31-50, 51-65, 66-75, and >76 years). Male and female cohorts were analysed separately. Descriptive analyses were performed with statistical software (Stata v15).

Results: Data for 929 MT cases (772 male, 78%) from 11 sites (6 Australian; 5 New Zealand) between Dec 2007-Dec 2017 were included. Median age [interquartile range] of males was younger than females, 44 [28, 59] vs 50 [33, 67] years respectively ($p<0.001$). Proportion of patients >65-years was 15.7% for males and 27% for females ($p=0.0003$), with pedestrian injury the most prevalent mechanism for females >65-years (40%). Mortality was higher for patients >65-years compared to ≤65-years (41.7% vs 23.9%; $p<0.0002$) and highest for females >76-years (53%). More than one-third of patients suffered a traumatic brain injury; of these, 46.2% died, with no significant difference between sexes. There were no significant differences between Australian and New Zealand MT cases for any variable.

Conclusion: Our findings provide insight into the demographic profiles of adult trauma patients who required emergency MT. Older trauma patients are a small, but significant, subgroup with increased adverse outcome.

10.03

Hepatic iron overload in transfusion dependent children

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Background: Regular transfusion is a highly effective and well-established treatment for a spectrum of erythrocyte disorders in Paediatric Haematology. Consequent iron overload is a common complication and requires accurate assessment to mitigate toxicity. Ferritin measurements are non-specific and liable to inflammatory and other changes, whilst liver biopsy is invasive, subject to significant sampling variability, and impractical for serial assessment.[1] Non-invasive measurement of iron in children using a spin-density projection-assisted R2-MRI technique (FerriScan®) is a well-recognised method used to assess iron overload in these patients.[2]

Aim: To determine the degree of correlation between iron load quantified using FerriScan® and our chelation practice.

Method: A retrospective cohort study was undertaken of all children admitted to the Haematology-Oncology ambulatory unit at Perth Children's Hospital for regular erythrocyte transfusions between July 2019 and June 2020. Medical record review provided diagnoses, age, weight, total transfusion volume, iron chelation regimen, and serum ferritin levels, with liver iron content established using FerriScan®. Linear and exponential regression analysis to determine any association(s) was completed.

Results: Of 22 transfused patients, 16 underwent FerriScan®. High iron load quantified using FerriScan® was only moderately correlated with chelation dosage, whilst ferritin levels were highly correlated with chelation practice in our cohort. Both FerriScan® and ferritin levels were correlated with total annual transfused erythrocyte volume, but not strongly correlated with each other; consistent with each marker measuring different aspects of iron load.

Conclusion: Optimal management in paediatric transfusion dependent anaemia requires careful consideration of patient factors, and choice of transfusion and chelation regimen. Our chelation prescribing practice is well correlated to ferritin levels, however there is potential for further improvement with greater responsiveness to FerriScan® results. An Australasian paediatric guideline incorporating iron load assessment and chelation recommendations for transfusion dependent children is currently lacking and could effectively guide best management.

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10.04

Frequency and risk factors for red blood cell allo-antibodies in critical bleeding/massive transfusion patients

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Aim:
Determine the frequency of, and risk factors for, pre-existing, anamnestic, or new RBC allo-antibodies in patients with critical bleeding (CB) undergoing massive transfusion (MT, defined as ≥5 RBC transfused in a 4h period).

Methods:
Data were extracted from the Australian and New Zealand (NZ) Massive Transfusion Registry (ANZ-MTR) on 2585 adult NZ patients with CB/MT during 2011-2019. Data obtained included date and time of MT initiation, clinical bleeding context, demographics, blood group and RBCs transfused. RBC allo-antibody results and dates were obtained from the New Zealand Blood Service. Allo-antibody type was determined from the time the antibody was detected in relation to MT initiation. We calculated summary statistics, odds ratios (OR) for potential risk factors for antibody formation, and immunogenicities of selected RBC antigens (i.e. relative abilities to provoke allo-antibody responses).

Results:
No antibodies were found in 1166/1229 (94.9%) assessable patients. Pre-existing, anamnestic, or new antibodies were found respectively in 102/2390 (4.3%), 5/1329 (0.4%), and 95/1314 (7.2%) patients. The five most common pre-existing antibodies were antibody of undetermined specificity, AUS (30.4%), anti-E (8.8%), probable passive anti-D (7.8%), anti-K/-Fy^a. (5.9% each). The five most common new antibodies were AUS (20%), anti-K (13.7%), anti-E (9.5%), anti-Jk^a (6.3%), anti-E+AUS/anti-low-incidence antigen (5.3% each). Statistically significant associations with new allo-antibodies were male sex and trauma. The quantum of RBC transfusion appeared to be a predisposition to, and obstetric haemorrhage protective against, new antibody formation, but ORs for both were not statistically significant. The immunogenicity of Jk^a appeared to be the highest in this setting.

Conclusion:
We found RBC allo-antibodies of any type to be uncommon in CB/MT patients who appeared to have lower risks of re-stimulating anamnestic antibodies, and of developing new antibodies, than other transfused patients. This information will be useful in the transfusion management of CB/MT patients.

10.06

A tailored approach to reducing apheresis platelet use in Western Australia

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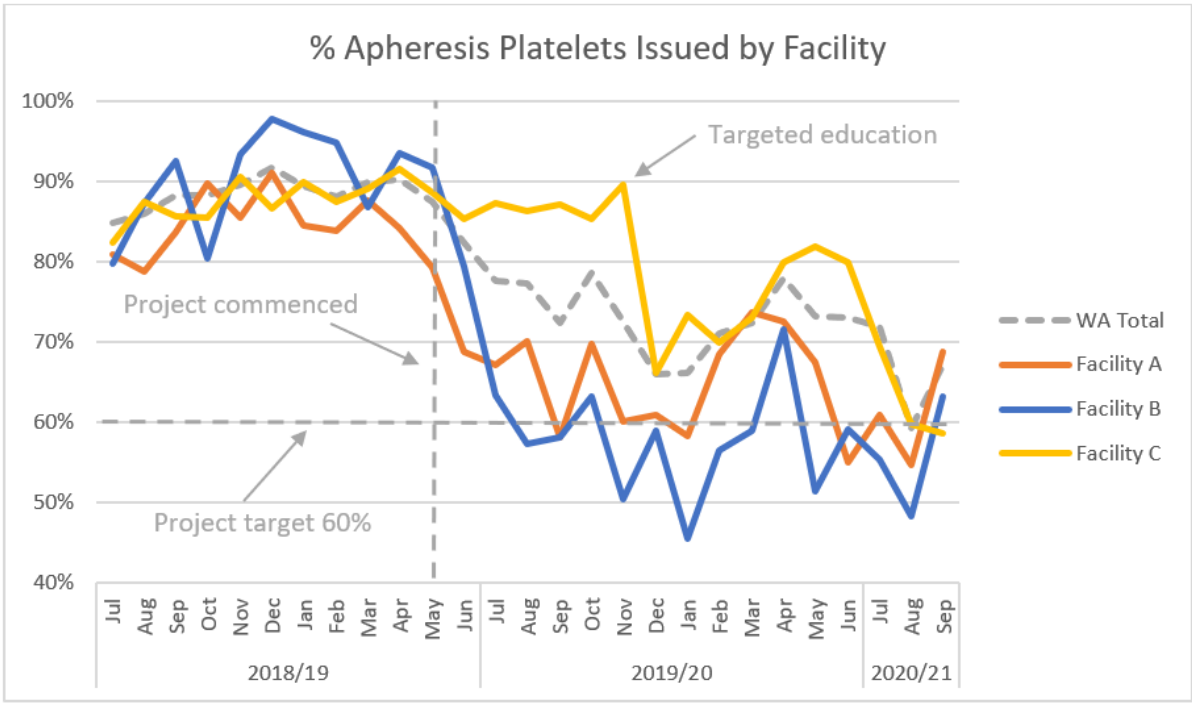
Aim: The primary aim of this project was to reduce the demand on apheresis platelets within Western Australia (WA). In 2018/19, eighty six percent of platelets issued to the three main tertiary hospitals in WA were apheresis. In recent years, advances in pooled platelet collection, processing and testing has resulted in a pooled platelet product that is the equivalent of apheresis platelets for most clinical indications. In Australia, pooled platelets are fifty nine percent less expensive to manufacture than apheresis platelets. In 2019, the Office of the Chief Medical Officer (OCMO) Blood Unit established a project to reduce apheresis platelet use within WA to sixty percent.

Method: Formal letters from the Chief Medical Officer were sent to hospital blood management committees outlining the project aims and providing current evidence of the clinical equivalence of pooled and apheresis platelets. Facilities that requested apheresis platelets as standard practice were identified and targeted education provided. Platelet data was also provided to hospitals to facilitate the development of internal benchmarks. Targeted education was provided to reduce the requesting of generic platelets when apheresis platelets were not clinically required.

Results: In 2019/20, the percentage of apheresis platelets issued to the three main tertiary hospitals decreased to 69%. This represents a cost saving of $673,973 (18%) to WA and the Commonwealth. There was no observed impact on patient outcome and no significant change in the number of reported adverse reactions to platelet products. ARCBS Lifeblood reported no issues with their ability to supply the requested platelet products.



Conclusion: Tailored strategies to promote the use of pooled platelets have been effective in reducing the dependence on apheresis platelets at tertiary hospitals within WA. This has resulted in a significant cost saving without impacting on patient outcome and represents a more balanced and sustainable use of platelets within WA

10.07

A case of HDFN defines a novel low frequency Rh antigen associated with Indigenous heritage and identified in a blood group genomic study

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Aim: In 2015 an Australian woman (35 years) of Indigenous heritage gave birth to a full-term baby. Soon after the baby was treated for haemolytic disease of the fetus and newborn (HDFN).

To apply serological-/genomic studies for an unresolved HDFN case with Indigenous heritage

Method: Immunohematology work-up was performed on samples from the mother, father (also Indigenous) and infant. Genomic-based sequencing used a targeted blood group exome panel with the IIlumina MiSeq platform.

In 2020 a collaborative Indigenous Australian study investigated genomic and blood group serology profiles for 245 participants presenting at Toowoomba.

Results: The mother (phenotype: D+C+c+E-e+) and infant (D+C+c-E-e+) were group A, compatible. The neonate's direct antiglobulin test (DAT) was positive with monospecific anti-human (AHG) IgG. Both maternal plasma and antibody eluted from infant cord reacted with paternal red cells.

Maternal plasma was compatible with all panel red cells tested suggesting the mother had an antibody against a low frequency antigen on the paternal and infant red cells. The paternal red cells (D+C+c+E+e+) tested negative for a panel of known low frequency antigens.

Sequencing implicated a novel single nucleotide variant (c.486C>G) on the *RHCE* allele for the father and infant which predicts an amino acid change (p.N162K) in the third extracellular domain of the RHCE blood group protein.
The Indigenous genomic study revealed two subjects (2/245) hemizygous with the c.486C>G allele. Maternal plasma stored from 2015 was reactive against both subjects' red cells. These findings indicate that *RHCE*c*.486C>G generates a novel LFA.

Conclusion: For pregnancy management, maternal alloantibodies against red cell antigens can go undetected during antenatal screening if the corresponding antigen is not represented on the reagent red cell panels. We define a novel Rh antigen in the Indigenous population. Further population studies may recommend that such antigens should be included in red cell screening panels.

Acknowledgements:
We acknowledge and pay respects to the First Nations Peoples of Australia who took part in this study. We are grateful for the opportunity to work together and the trust placed in us to undertake research in a respectful and collaborative manner.
This study was conducted in collaboration with the Carbal Medical Services in Toowoomba in consultation with the Indigenous Community Advisory Committee and under the approval of the Australian Red Cross Lifeblood Human Research Ethics Committee.
Australian governments fund the Australian Red Cross Lifeblood to provide blood, blood products and services to the Australian community.

10.08

EveryOne counts: a retrospective cohort study evaluating safety of extending pre-transfusion compatibility testing

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Aim: This project aims to investigate the safety of extending the pre-transfusion compatibility testing (PTCT) interval from 72-hours to 7 days in Haematology patients receiving PRBC. We hypothesise that the rates of acute and delayed transfusion reactions will be similar before and after the protocol change.

Method: All transfusions from haematology patients from 1 July 2017 and 30 June 2019 were exported from blood management software eBlood. A total of 1,981 packs were analysed from 243 patients. Transfusions prior to 1 July 2018 were only eligible for a 72 hour PTCT interval. The period from 1July 2018 was considered post intervention as transfusions were eligible for up to a 7 day PTCT interval. The primary outcome was the incidence of transfusion reactions with pre-post intervention analysis.

Results: Acute leukaemia was the most common diagnosis across both groups (30.22% of patients in pre-protocol change and 31.73% in post-change). There was an even distribution of male and females in both groups. (45.32% female in pre-protocol group compared to 47.12% in post-protocol group). There were 6 (0.30%) transfusion reactions across the study and all were acute. These reactions all occurred within the post-protocol change cohort (0.74%), although all had a PTCT interval of < 72 hours. No reactions occurred within the pre-protocol change cohort (0.00%). These occurred during 4 discrete events, each unique patients. (see figure 1)

Figure 1

	Age	Gender	Diagnosis	Chronically transfused*	PTCT Interval (Hours)	Units Given	Known Antibodies	Antibodies detected	Acute Transfusion Reaction
1	57	M	ALL	YES	20.87	2	Nil	Nil	Rigors
2	68	M	ALL	YES	23.82	1	Nil	Nil	Paraesthesia and vomiting
3	69	M	AML	YES	24.28	2	Nil	Nil	Febrile
4	27	M	NHL	YES	6.10	1	Nil	Nil	Rigors

* Chronically transfused is defined as >6 transfusions in a 12-month period

Conclusion: This study found no evidence for an increased risk of transfusion reactions associated with increasing the PTCT interval from 72 hours to 7 days. Extending the PTCT interval has the potential to decrease physical and human resource burden, decrease patient infection risk, improve patient comfort and conserve public health resources. More research is needed to further validate 7 days as a safe duration for PTCT in Haematology patients.

10.09

RBCeq: A Robust and Scalable Algorithm for Accurate Genetic Blood Typing

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Aim: Safe blood transfusion is an essential cornerstone of haematological supportive care. Repetitive blood transfusion increases the risk of red cell alloimmunisation in patients which can impact on the timeliness antigen negative blood provision to prevent adverse transfusion outcomes. Despite the promise, user-friendly method for accurate blood typing from next-generation sequencing data is currently lacking. To address this unmet need, we have developed RBCeq, a novel genetic blood typing algorithm.

Method: Blood groups profiling is divided into three steps 1) Extract single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) from NGS data; 2) Genotyping and phenotyping of the known blood groups alleles from SNPs and CNVs data using a developed novel algorithm and curated database; 3) In-silico prediction of novel and rare blood groups variants that may encode for novel antigens. All three steps are integrated into a user-friendly web application called RBCeq (https://www.rbceq.org/).

Results: RBCeq is an automated web server-based (https://www.rbceq.org/) software with advanced visualization capabilities and the ability to address the computational and storage challenges associated with large NGS data processing. It profiles 36 blood groups and identifies genomic alterations like indels and CNVs. The RBCeq algorithm was validated on 403 serologically tested samples which include 58 complex serology cases from Australian Red Cross LifeBlood, 100 samples from The MedSeq Project and a further 244 from Indigenous Australian participants. The final blood typing data from RBCeq was 99.40% concordant for 402 samples (85 different antigens in 21 blood group systems) with that listed from the ISBT database. RBCeq provides fast and accurate mass screening for rare and complex blood group profiles within diverse populations and markedly reduced the time required for pre-transfusion testing, thereby increasing sample processing throughput.

Conclusion: RBCeq will assist blood banks and immunohematology laboratories by overcoming existing methodological limitations like scalability, reproducibility, and accuracy when genotyping and phenotyping in multi-ethnic populations. This platform has the potential to reduce pre-transfusion testing time and to increase sample processing throughput, ultimately improving the quality of patient care.

10.10

Freeze-drying Oxidised Human Red Blood Cells for Blood Group Serology Diagnostics

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Aim: The aim of this study is to determine whether (1) oxidative pre-treatment of red blood cells (RBCs) before rapid freeze-drying preserves RBCs; and (2) oxidised freeze-dried RBCs (oxFDRBCs) are an alternative source of reagent RBC for alloantibody serology tests.

Method: Fresh human RBCs were treated with oxidant (n=6), tert-butyl-hydroperoxide (0.5 mM, 35 mins), freeze-dried for 2.5hr. After 2 weeks of desiccated storage at room temperature (RT), oxFDRBCs were rehydrated and the lipid integrity and metabolism were characterised by flow cytometry and confocal microscopy. Cell mechanical properties were evaluated using rheology analysis. Cell morphology was assessed by scanning electron microscopy (SEM), and blood group typing was performed by column agglutination technology (CAT).

Results: The recovery rate of rehydrated oxFDRBCs was >85%. oxFDRBCs showed alteration of morphological shape, lipid integrity, metabolism, and cell rigidity. RBC oxidised with 0.5 mM TBHP has by 30% of normal RBC size (5.5 µm-7.5 µm) and by 57% of reduced size (3.5 µm-5.5 µm). oxFDRBC retained by of 61% the metabolism activity and by 40% of the lipid integrity. oxFDRBCs retained for ABO and Rhesus-D blood group reactivity by CAT tests.

Conclusion: Mild-oxidation of RBCs immediately before freeze-drying appears to be protective by stabilising the RBC membrane. oxFDRBCs could be a future source of reagent RBCs for blood group serology testing in remote areas were transport and infrastructure resources, such as reliable refrigeration, are limited.
''No conflict of interest to disclose''

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10.11

Molecular Characterisation of Monocyte Responses to Sensitised Red Blood Cells to Delineate Mechanisms Underpinning the Monocyte Monolayer Assay

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Background and Aims: The monocyte monolayer assay (MMA) is used to predict the clinical significance of red cell antibodies and inform transfusion decision making. The assay is technically demanding, laborious and difficulties with reproducibility and sensitivity have been reported. The mechanisms of interaction between immune cells and clinically significant or non-significant antibodies remain largely undefined. We aimed to characterise monocyte activation and interaction with sensitised RBC at the molecular level to improve our understanding of the underlying mechanisms associated RBC clearance with and inform methods to improve prediction of the clinical significance of RBC antibodies.

Method: MMA was used to select two clinically significant (Anti-D, Monocyte Index (MI) 44%; Anti-K, MI 25%) and two non-clinically significant antibodies (Anti-Ch, MI <3%; anti-JMH, MI <3%) to further characterise changes in monocyte responses using a molecular approach. Following a modified cell culture plate MMA based protocol, RNA was isolated from monocytes for cDNA synthesis, pre-amplification and RT-PCR of 48 genes involved in cell activation, intracellular signalling and immune response using the TaqMan Gene Expression Array Cards (Applied Biosystems). Gene expression was compared to matched saline controls (one-way ANOVA with Dunnett's post-test; $P<0.05$).

Results: Exposure to sensitised RBC resulted in monocyte upregulation of genes involved in cell adherence (CD9, ICAM-1), cell recruitment (CCL4, CCR5) and immune regulation (TGFB1, IL-1A, TNF) regardless of whether the classification of the antibody was clinically, or nor non-clinically significant. Monocytes exposed to RBC sensitised with clinically significant antibodies differentially upregulated genes involved in CD32 driven receptor binding (FCGR2C), cytoskeletal arrangement (RHOA, RAC-1) and chemotaxis (CCL3, CCR5).

Conclusion: Using a molecular approach, we characterised monocyte interactions with sensitised RBC in an MMA based system. We provide preliminary evidence that molecular techniques applied to determine the clinical significance of antibodies directed against RBC.

10.12

What's in the bag? - Do residual progenitor cells remain following leucodepletion of red blood cell units

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Aim: Despite the use of leucodepleted red blood cell (RBC) units for transfusion, we have shown that donor leucocyte engraftment (transfusion-associated microchimerism (TAM)) remains a long-term transfusion related outcome in some patient groups. The mechanism of how TAM can occur is unknown. Therefore this study aimed to isolate and characterise any residual cells from leucodepleted RBC units.

Method: RBC units were manufactured using standard Australian Red Cross Lifeblood methods. Two RBC units were analysed at each storage timepoint of day 1, day 7, day 14, day 21 and day 42 post-collection. Residual cells were isolated from leucodepleted RBC units using EasySep™ RBC Depletion Reagent (StemCell Technologies). Residual cell pellets were stained with BD Leucocount™ reagent and also with anti-CD45 and anti-CD34 antibodies (BD Biosciences). Cell viability was determined using 7AAD. Residual cell pellets were characterised and enumerated by flow cytometry (BD FACSCanto™ II) using BD Trucount™ tubes (BD Biosciences).

Results: The residual cell pellets were stained with the Leucocount™ reagent to confirm that leucocytes were present at each of the tested storage timepoints and were found to be present ranging from 0.1 cells/µL to 3.4 cells/µL. Analysis using anti-CD45 and anti-CD34 antibodies indicated that viable CD34+ cells were present at each storage time point ranging from 0.2% to 1.8% of CD45+ events.

Conclusion: Despite the use of leucodepletion, viable residual progenitor cells remain present in manufactured RBC units and transfused patients may be exposed to these cells. This finding provides a potential mechanism for understand why long-term transfusion related outcomes such as TAM, may occur.

Australian governments fund Australian Red Cross Lifeblood to provide blood, blood products and services to the Australian community.

11. THANZ Free Communications

11.01

Treatment of ITP- a Multi-Centre Retrospective Review

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Aim: In Australia prescribing restrictions limit access to internationally recommended second line therapies such as Rituximab and thrombopoietin agonists (TPO-A) (eltrombopag and romiplostim). Subsequent lines of therapy include an array of immunosuppressive agents directed by drug availability and physician preference. This study compares the usage, response rates and side-effect profiles of first and second-line treatment for ITP.

Method: A retrospective review of medical records was conducted of 322 patients treated for ITP at 8 participating centres in Australia between 2013 and 2020. Data was analysed by descriptive statistics and multivariate analysis using pivot tables and compared between centres using paired t-tests.

Results: Mean age at diagnosis of ITP was 48.8 years SD 22.57. 58.30% were female. 234/322 (72%) had primary ITP, and 88/322 (28%) secondary ITP. 95.1% of patients received first-line treatment with prednisolone (76%), dexamethasone (15%) or intravenous immunoglobulin (IVIG) (48%) alone or in combination. Individuals with secondary ITP were less likely to be steroid-dependent (72% vs. 76%), less likely to require treatment with a second line agent (47% vs. 58%)

56% of the cohort (181/322) received treatment with one or more second-line agents. The mean number of second-line agents used for each patient was 1.87 SD 1.17. The most commonly used second-line therapy was Rituximab, followed by Eltrombopag and splenectomy. These also generated the highest rates of complete response (60.32%, 72.09% and 71.79% respectively). The most unfavourable side-effect profiles were seen in long-term corticosteroids and splenectomy. Cyclophosphamide and Danazol were infrequently used.

	Number of patients on drug	Complete Response	Response	No Response	Portion of patients Experiencing side effects
Azathioprine	23	34.78%	39.13%	26.09%	13.04%
Combination/Other	54	51.85%	37.04%	11.11%	33.33%
Cyclophosphamide	2	0.00%	50.00%	50.00%	50.00%
Danazol	1	100.00%	0.00%	0.00%	0.00%
Dapsone	35	40.00%	25.71%	28.57%	25.71%
Dexamethasone	13	23.08%	69.23%	7.69%	46.15%
Eltrombopag	43	72.09%	23.26%	4.65%	11.63%
Mycophenolate	10	30.00%	60.00%	30.00%	10.00%
Rituximab	63	60.32%	15.87%	20.63%	6.35%
Romiplostim	37	59.46%	18.92%	18.92%	16.22%
Splenectomy	39	71.79%	17.95%	10.26%	33.33%

Table 1. Rates of response and side effects for second-line agents

Conclusion: A wide range of "second-line" agents are used across centres with variable response rates and side effect profiles. Our results confirm the efficacy of Rituximab and TPO-A supporting their use earlier in the treatment course of patients with ITP across Australia.

11.02

Anti-platelet Antibody's Differential Impact in ITP

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Aim: Immune thrombocytopenia (ITP) is a bleeding disorder. The pathogenesis involves antibodies recognising membrane glycoprotein (GP) complexes, mainly GPIbIX and GPIIb/IIIa. In addition to the current view of phagocytosis by splenic and hepatic macrophages, antibody-induced platelet desialylation and apoptosis have also been reported. We aim to establish if an association exists between antiplatelet antibody specificities and the various thrombocytopenic mechanisms in ITP.

Method: The study was approved by Human Research Ethics Committee of UNSW. We examined sera from 61 ITP patients for the presence of detectable antiplatelet antibodies by flow cytometry. Antibody specificity was determined by monoclonal antibody immobilisation of platelet specific antigen assay (MAIPA). We used donor platelets to assess the capacity of antibody to induce platelet desialylation by determining surface expression of neuraminidase 1 (NEU1) and RCA-1 lectin binding, as well as platelet apoptosis by measuring the loss of mitochondrial inner membrane potential (DiOC6). To evaluate the impact of the Fc pathway, the assays were performed in donor platelets pre-treated with Fc RIIA inhibitor.

Results: Sera from ITP patients with detectable antibodies caused significant platelet NEU1 surface translocation and reduced DiOC6 signal, indicating the presence of platelet desialylation and apoptosis, respectively (Kruskal-Wallis test with Dunn's multiple comparison). In contrast to previous literature, anti-GPIIb/IIIa antibodies appeared more capable in causing NEU1 surface translocation (67% of patients) while 80% of sera from patients with anti-GPIbIX antibodies induced platelet apoptosis. Both processes appeared to be dependent on the Fc pathway, not platelet activation.

Conclusion: We report the predictive capability of antiplatelet antibody test in relation to the potential underlying ITP mechanisms and demonstrate the differential influence of antibody subtypes on the downstream effect on platelet survival. We suggest ITP antibody testing to be incorporated into ITP management algorithm as it potentially guides treatment individualisation.

11.03

Identification of a distinct platelet phenotype in the elderly: ADP hypersensitivity co-exists with platelet protease-activated-receptor (PAR)-1 and PAR-4 mediated thrombin resistance.

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Aim: Thrombin (via PAR-1 and PAR-4 receptors) and adenosine diphosphate [ADP] (via $P2Y_{12}$ receptors) are potent endogenous platelet activators implicated in the development of cardiovascular disease (CVD). While the frequency of CVD increases with age, the benefit of antiplatelet agents diminishes in the elderly. We aimed to assess whether platelet pathways altered with ageing.

Method: We characterised platelet activity in community-dwelling volunteers (n=174) recruited at Concord Hospital, Sydney, in the following age groups: (i) 20-30 (young); (ii) 40-55 (middle-aged); (iii) ≥70 years (elderly). Platelet activity was assessed by whole blood aggregometry; flow cytometry (surface markers [P-selectin: alpha granule release, CD63: dense granule release, PAC-1: GPIIb/IIIa conformational activation] measured under basal conditions and after agonist stimulation [ADP, thrombin, PAR-1 agonist or PAR-4 agonist]; receptor cleavage and quantification; fluorometry; calcium flux; ELISA.

Results: The elderly had higher basal platelet activation than the young, evidenced by increased expression of P-selectin, CD63 and PAC-1, which correlated with increasing inflammation (interleukin-1β). The elderly demonstrated higher $P2Y_{12}$ receptor density, greater ADP-induced platelet aggregation and lower stored intracellular ADP (all $p<0.05$). However, elderly subjects were resistant to thrombin, achieving less activation in response to thrombin (higher EC_{50}) and to selective stimulation of both PAR-1 and PAR-4, with higher basal PAR-1 and PAR-4 receptor cleavage and less inducible PAR-1 and PAR-4 cleavage (all $p<0.05$). Thrombin resistance was attributable to a combination of reduced thrombin orienting receptor GPIbα, reduced secondary ADP contribution to thrombin-mediated activation and blunted calcium flux. D-Dimer, a marker of *in-situ* thrombin generation, correlated with platelet activation in the circulation, *ex-vivo* thrombin resistance and circulating inflammatory mediators (TNF-α).

Conclusion: Ageing is associated with a distinctive platelet phenotype of increased basal activation, ADP hyperreactivity and thrombin resistance. *In-situ* thrombin generation associated with systemic inflammation may be a novel target to prevent and treat CVD in the elderly.

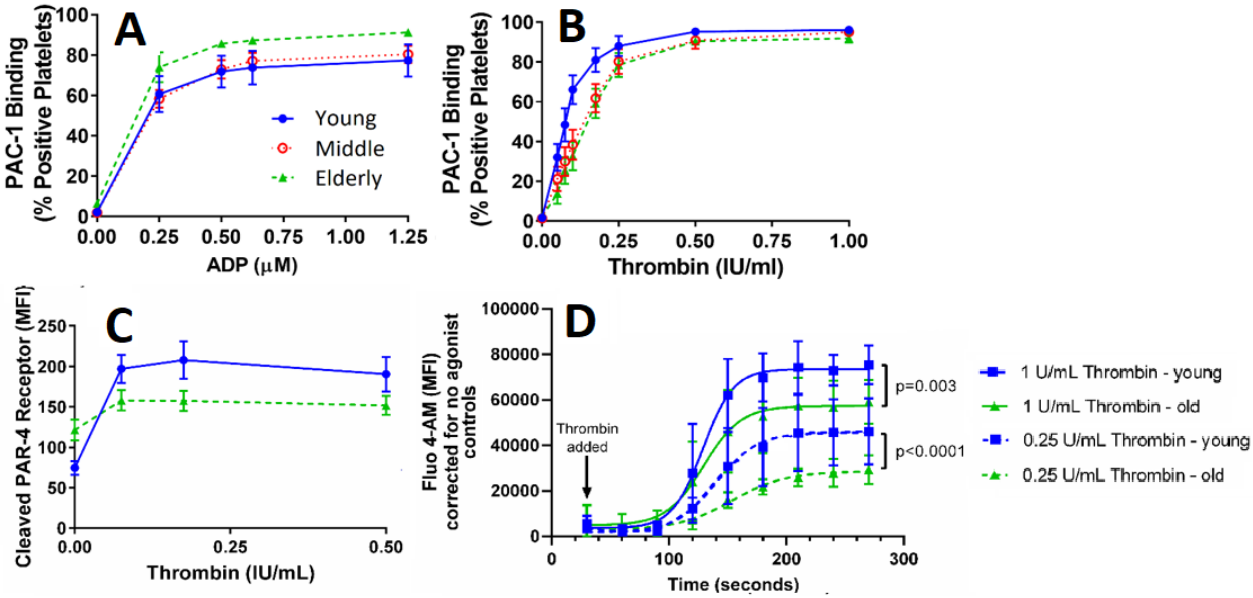

Figure 1: Age-related changes in platelet activatation. (A) PAC-1 binding after ADP stimulation; (B) PAC-1 binding after thrombin stimulation; (C) Cleaved PAR-4 receptor MFI post thrombin; (D) Calcium flux in response to thrombin (0.25 and 1 U/mL) in the young group versus the old group, platelet rich plasma.

11.04

A case series of venous thromboembolism and individualising management in transgender individuals on hormone therapy.

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Aim: Gender affirming hormone therapy is increasingly utilised in transgender individuals. In cis women, exogenous oestrogen is a well-recognised thrombotic risk in a dose-dependent manner. This risk is heightened in the presence of other venous thromboembolism (VTE) risk factors like inherited thrombophilia and obesity. In contrast, the prothrombotic risk of testosterone replacement is less established.

Theoretically, the VTE risks of hormone therapy would apply to transgender individuals. However, the prevalence of VTE during hormone therapy and how the risk changes over time within the transgender population remain unknown. There is a need to further understand this in the transgender population to guide VTE risk stratification and management.

Method: The clinical features and management of VTE in four transgender individuals are reported.

Results: Patients 1 to 4, aged 31, 38, 43 and 53 years respectively, developed VTE during hormonal therapy. Patient 1 developed lower limb deep vein thrombosis (DVT) after one month of transdermal oestradiol. Patients 2 and 3 were on oral oestrogen therapy and Patient 4 on intramuscular testosterone for Klinefelter syndrome (all were on therapy for >12 months) when they developed VTE. Patients 2 and 4 had pulmonary emboli and DVT. Patient 3 developed DVT in the context of increasing her oestradiol dose and previously provoked DVT following gender reassignment surgery.

All patients were anticoagulated: Patient 1 with warfarin, and Patients 2 to 4 with direct oral anticoagulants. Long-term care were individualised with Patient 2 electing to discontinue hormonal therapy after 6 months due to concerns regarding alopecia from her anticoagulation. Patient 4 has ceased her testosterone replacement and commenced oestrogen as part of transition therapy.

Conclusion: These cases affirm the prothrombotic risk of exogenous hormone therapy and complex long-term VTE management of transgender individuals. Larger studies are needed to further our understanding of VTE risk and improve the care of transgender individuals

11.05

Pulmonary embolism response team (PERT) for intermediate to high-risk pulmonary embolism- Outcomes of the first Australian model of care

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Aim: Pulmonary Embolism (PE) is a major cause of morbidity and mortality in Australia[1]. In 2018, we formed the first Australian PE response team (PERT), in line with 2019 European Society of Cardiology (ESC) Pulmonary Embolism (PE) Guidelines [2], to provide timely, multidisciplinary management of PE. We aimed to evaluate the clinical characteristics, risk stratification, management and outcomes of high/intermediate-high risk PE patients treated using the PERT model.

Method: We performed a retrospective review of PERT-managed patients at our institution between July 2018 - June 2020, compared with a historical cohort of 28 consecutive patients (pre-PERT) identified by ICD-10 codes. Patients were stratified into intermediate-high/ high risk according to ESC Guidelines[2], including RV:LV ratio before and after catheter-directed thrombolysis (CDT). Management outcomes included reperfusion modality (systemic or CDT, suction thrombectomy), bleeding complications and 30-day mortality. Statistical analysis was performed using Fisher's exact tests.

Results: 52 patients were PERT managed; see Table 1 for clinical characteristics. Compared to pre-PERT, more PERT patients were high (18% *vs* 21%, p= 0.779) and intermediate-high risk for mortality (14% *vs* 60%, p= 0.0001). Risk stratification was incomplete in pre-PERT patients with fewer echocardiographic assessments for RV dysfunction (57% *vs* 92%, p= 0.0003). Intervention with historical compared to PERT patients included CDT (4% *vs* 69%, p= 0.0001), suction thrombectomy (4% *vs* 15%, p=0.150), systemic thrombolysis 4% *vs* 21%, p= 0.014) and IVC filter (4% *vs* 27%, p= 0.056). RV ratio improved in 16/17 patients post CDT from 1.41 (0.25) to 1.07 (0.14); p = <0.0001. Serious bleeding events (11% *vs* 10%, p= 1.0) and 30-day mortality rates (8% *vs* 3%, p=1.0) were comparable.

Conclusion: PE risk stratification and assessment for RV dysfunction was significantly increased using PERT. Intermediate/ high risk patients underwent successful reperfusion without increased haemorrhage or mortality. Patient outcomes using our PERT model of care are comparable to international data.

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Table 1: Clinical characteristics of pre-PERT *vs* PERT patients

Pre-PERT patients			PERT patients		
	N (%) or mean	Standard deviation	N (%) or mean	Standard deviation	p-value
Number	28		52		
Age	71 years	14 years	59.6 years	16.8 years	
Male Sex	17 (61%)		27 men (52%)		0.488
High risk for mortality	5 (18%)		11 (21%)		0.779
Intermediate-high risk	4 (14%)		31 (60%)		0.0001
Intermediate-low risk	19 (68%)		10 (19%)		0.0001
sPESI index*	2	1.19	1.8	1.2	
Elevated troponin	19 (68%)		48 (94%)*		0.0090
ICU/HDU LOS**	6.3 days	Range: 0-32 days	6 days	Range: 0-29	
TTE*** performed at baseline	16 (57%)		48 (92%)		0.0003

* sPESI: simplified pulmonary embolism severity index
** Intensive care unit/ High dependency unit length of stay
***Transthoracic echocardiogram

11.06

Effectiveness of DOAC-STOP™ in laboratory Lupus Anticoagulant testing for patients on DOAC therapy.

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Aim: Direct Oral Anticoagulants (DOACs) interfere with various Lupus Anticoagulant (LA) clotting tests. DOAC-STOP™ (Haematex, Australia) is a charcoal agent reported to extract DOACs from plasma during *in vitro* processing and allow LA testing to proceed to a valid result. Our aim was to verify the effectiveness of DOAC-STOP™ in local laboratory LA procedures.

Method: Nine plasma pools (with no suspicion of DOAC therapy) were prepared from LA negative, weak, intermediate and strongly positive patients respectively, also from patients on Heparin and Warfarin and healthy donors. Each pooled plasma was tested by dilute Russell's Viper Venom Time (dRVVT), Silica Clotting Time (SCT) and Kaolin Clotting Time (KCT). Tests were then repeated after *in vitro* addition of Rivaroxaban, Dabigatran and Apixaban (Haematex Inhibitor Dots at ~350mg/ml) and again after treatment with DOAC-STOP™.

Results: For each plasma pool, anti-Xa assays confirmed the expected levels of *in vitro* added DOAC, and their removal by DOAC-STOP™. For normal or negative pools spiked with Rivaroxaban or Dabigatran, all displayed false LA positivity by dRVVT, SCT and KCT. Treatment with DOAC-STOP™ consistently returned the dRVVT to a negative result but not always the SCT or KCT. The positive pools increased to higher positivity with either added Rivaroxaban or Dabigatran and returned to pre-treatment dRVVT after DOAC-STOP™ treatment, but not consistently the SCT or KCT. When adding Apixaban, the weak positive pool displayed false LA Negativity and the intermediate and strong LA had lessened positivity. Results for the dRVVT ratio returned to baseline post DOAC-STOP™ treatment. Falsely prolonged PT or APTT were also corrected.

Conclusion: This study shows DOAC-STOP ™is an effective solution to allow LA testing for the patient on DOACs and unable to cease therapy. LA diagnosis using DOAC-STOP™ treated plasma should be mainly based on dRVVT findings and not isolated SCT or KCT results.

11.07

Comparison of viscoelastic haemostatic assays for point of care coagulation assessment

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Background: Viscoelastic haemostatic assays are now considered the gold standard measurement for the assessment and management of coagulation abnormalities in perioperative and critical care settings. The latest iterations of the two most commonly used devices—TEG6s and ROTEM*Sigma*—have evolved to improve ease of use and are now cartridge-based. Despite being used interchangeably in clinical practice, the two cartridge-based systems have rarely been directly compared.

Methods: Patients undergoing cardiac surgery (requiring cardiopulmonary bypass) or interventional (transcatheter aortic valve implantation or percutaneous coronary intervention) were recruited prospectively. Blood samples (n=164) were obtained at four timepoints, depending on the procedure (baseline, post-heparin administration, post-protamine reversal, and six-hours postoperatively). Each sample was assessed concurrently for standard laboratory tests (PT/INR, aPTT, thrombin clotting time, platelet count, direct fibrinogen), complete+hep (ROTEM*Sigma),* and citrated (TEG6s) cartridges.

Results: For extrinsically-activated assays, a strong correlation existed for clot strength (MCF-EXTEM vs. MA-CRT, r=0.89), but not ‘time to initiation of clot formation’ (CT-EXTEM vs. R-CRT, r=0.34). For intrinsically-activated assays, strong correlations existed for both ‘time to initiation of clot formation’ (CT-INTEM vs. R-CK=0.81; CT-INTEM vs. R-CRT=0.89) and clot strength (MCF-INTEM vs. MA-CK, r=0.81; MCF-INTEM vs. MA-CRT, r=0.87). Particularly important for both cardiac surgery and trauma settings is that measurements of the fibrinogen contribution to clot strength were highly correlated (MA-CFF vs. MCF-FIBTEM, r=0.94) and correlated with standard laboratory fibrinogen levels (fibrinogen vs. MA-CFF, r=0.85; fibrinogen vs. MCF-FIBTEM, r=0.86). Poor correlation was evident assessing time of fibrin formation between the two systems’ heparinase channels (CT-HEPTEM vs. R-CKH, r=0.53) and clot strength (MCF-HEPTEM vs. MA-CKH, r=0.53).

Conclusion: Though ROTEM*Sigma*® and TEG6s® are strongly correlated in some measurements, they are poorly correlated in others, suggesting that their results, and therefore clinical use, are not interchangeable.

11.08

Acquired haemophilia A: insight into treatment and outcomes from an Australian tertiary referral centre.

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Aim: Acquired haemophilia A (AHA) is a rare autoimmune bleeding disorder associated with significant morbidity and mortality. Its rarity contributes to the limited data regarding characteristics and outcomes. We reviewed all cases of AHA managed at our institution, the state Haemophilia Treatment Centre, between 2010 and 2020.

Method: 38 patients were identified from our database. Data regarding demographics, diagnosis, bleeding episodes, treatment and complications were collected and analysed. Patients were followed from diagnosis to end of review.

Results: Baseline characteristics are outlined in Table 1. The mean duration between bleeding onset and diagnosis was 15 days (range 1-180). Over 70% presented with spontaneous bleeding and common locations were subcutaneous (36%) and intramuscular (13%). 63% of bleeding episodes were classified as severe; no association was found between FVIII level or FVIII inhibitor titre and bleeding severity. 89% of patients required haemostatic therapy, most commonly rFVIIa or a combination of agents. The majority of patients (86%) received a combination of prednisone, cyclophosphamide and/or rituximab as immunosuppressive therapy (IST) for inhibitor eradication. Median follow-up time was 46.5 months during which 87% achieved a complete remission (CR) and 30% relapsed at a mean of 345 days after initial remission. No association was found between any baseline characteristics (table 1) or IST regimen and likelihood of CR or relapse. 63% had ≥1 complication, which were more likely with combination IST. There were no deaths.

Baseline characteristics	**Data**
Male, n (%)	21 (55)
Median age, years (range)	73.5 (29-87)
Underlying diagnosis, n (%)	
None	17 (45)
Autoimmune	10 (27)
Malignancy	7 (18)
Postpartum	4 (11)
FVIII level (%), mean	5.4
FVIII inhibitor titre (BU/mL), mean	20.55

Table 1

Conclusion: This is the largest study of AHA in Australia reported to date. Our findings of delayed diagnosis, high complication rates and late relapses highlight the importance of improved awareness of AHA and continuing follow-up of patients.

11.09

Setting up a statewide service for laboratory testing of VITT (vaccine induced immune thrombotic thrombocytopenia) – a tertiary-hospital based laboratory experience

Ms Olivia Yacoub[1], *Dr Elizabeth Duncan[1], Mr Sunil Abraham[1], Mr Gerorge Giannakis[1], Mrs Joanne Apolloni[1], Ms Lis Burrows[1], Dr Vivien Chen[2], Dr CheeWee Tan[3], Dr Yvonne Brennan[3], Dr Uwe Hahn[3] [1]SA Pathology, Royal Adelaide Hosital, Adelaide, Australia, [2]ANZAC Research Institute, University of Sydney, Concord Hospital, Sydney, Australia , [3]Haematology Unit, Royal Adelaide Hospital, Adelaide, Australia*

Aim: VITT is a rare side effect of Astra Zeneca COVID-19 vaccination, characterised by thrombocytopenia, a significantly raised D-dimer, low fibrinogen and thrombosis in unusual sites. It can cause significant morbidity and mortality, making early diagnosis important. VITT shares similarities with heparin-induced thrombocytopenia(HIT). Certain laboratory tests for HIT, but not all, can be useful in detecting VITT, such as ELISA directed against PF4 antibodies. We set out to quickly establish a state-wide service, enabling clinicians to request important screening and confirmatory tests with suspicion of VITT.

Method: Two specific order sets were created, the first a screening set comprising platelet count, INR, APTT, D-dimer and fibrinogen; the second a confirmatory set for ELISA (Stago Asserachrom) as well as sample storage for functional assay testing (SRA and flow cytometry). Screening tests were reviewed with clinical information before progression or not to ELISA +/- functional testing. We assessed other HIT tests i.e.Acustar chemiluminesence and STIC Expert.

Results: Laboratory testing of VITT has been in place for 6 weeks. ELISA testing has been performed on 12 samples with a further 11 excluded from requiring ELISA. In three cases ELISA results have been positive, and concordant with likely pre-test probability of VITT based on clinical information, fibrinogen, D-dimer and platelet count. These were not detected by Acustar chemiluminesence or STIC. In samples with results for functional testing, there has been concordance of ELISA with functional assay, both with positive and negative results.

Conclusion: Clinical information, screening tests and ELISA are all important in the diagnosis of VITT. Results have been concordant to date between screening, ELISA and functional assay results. Discordance may emerge and will be captured and investigated. A streamlined approach to screening and confirmatory testing is important to manage laboratory resources and provide timely diagnosis/exclusion of VITT.

11.10

Overall Haemostatic Potential identifies greater severity of COVID-19 infection

Mr Niki Lee[1], *Dr Rowena Brook*[1,3], *Dr Kay Weng Choy*[1,3], *Dr Hui-Yin Lim*[1,2,3], *A/Prof Prahlad Ho*[1,2,3], *Dr Julie Wang*[1,2,3]
[1]Northern Health, Epping, Australia, [2]University of Melbourne, Parkville, Australia, [3]Northern Pathology Victoria, Epping, Australia

Aim: Identifying patients at risk of severe COVID-19 infection is important to aid in clinical decision-making. We hypothesized that the Overall Haemostatic Potential (OHP) assay may be useful for this purpose.

Method: Subjects were COVID-19 positive adult patients admitted to our institution between 31/3/2020 and 29/9/2020. The first citrated blood sample collected as part of routine care during the admission was double centrifuged and resultant platelet poor plasma (PPP) analysed by the OHP assay, in which fibrin generation and fibrinolysis is measured spectrophotometrically at 405nm. The overall coagulation potential (OCP) is the area under the time-curve of PPP activated by thrombin. The OHP is determined by the addition of tPA (350ng/mL) and thrombin to a parallel plasma sample. The overall fibrinolysis potential (OFP) is calculated by .

Results: Samples were collected from 105 COVID-19 patients, at median 2.3 days (range 0-19 days) after COVID-19 PCR positivity. Mean OHP in this cohort was markedly higher than mean OHP of previously collected normal control subjects (19.4 vs 7.3, p<0.001). Patients with OHP in the highest tertile, compared with those in the lowest tertile displayed significantly higher markers of inflammation including fibrinogen, C-reactive protein (CRP), lactate dehydrogenase (LDH) and ferritin (Table 1). D-dimer was not significantly different. Higher OHP was associated with more severe clinical course and these individuals were more likely to require intensive care unit (ICU) admission, assisted ventilation, glucocorticoids and antibiotics. Patients who received ventilatory support (high-flow oxygen, non-invasive and invasive ventilation) had significantly higher OHP compared to non-ventilatory supported patients (28.7 vs 17.7, p<0.001). Age, therapeutic anticoagulation or COVID-related death were not significantly different between groups.

Conclusion: Higher OHP at presentation with COVID-19 infection appears to correlate with a more clinically severe course. The OHP assay can be a rapid test to identify patients who may need more intensive therapeutic support and monitoring.

Table 1

	OHP lowest tertile N=37	OHP highest tertile N=37	p-value		OHP lowest tertile N=37	OHP highest tertile N=37	p-value
Age (years)	69.6	62.9	0.18	CRP (mg/L)	37.2	116.5	<0.001
Male	40%	56.8%	0.13	Ferritin (ug/L)	385.1	1180.3	0.001
Diabetic	17%	54%	<0.001	LDH (U/L)	227.5	419.1	<0.001
Weight (kg)	70.3	89.9	0.004	Respiratory rate >22	26%	59%	0.003
Therapeutic anticoagulation	43%	51%	0.47	Lung consolidation	37%	65%	0.008
D-dimer (mg/L)	1.0	1.9	0.22	ICU	6.0%	22.0%	0.05
Fibrinogen (g/L)	4.3	7.4	<0.001	Antibiotics	49%	76%	0.02
White cell count				Glucocorticoids	34%	70%	<0.001
Neutrophils ($x10^9$/L)	4.5	6.7	0.007	Assisted ventilation	3%	19%	0.02
Albumin (g/L)	34.6	27.3	<0.001	Death	20%	16%	0.68

11.11

Thromboinflammatory response in hospitalized patients with COVID-19; a single institution experience

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Aim: Up to 15% of patients with COVID-19 develop a severe inflammatory response to the virus which compromises lung function and other systems such as coagulation. The aim of this study was to study the time course of coagulation and inflammation parameters in patients hospitalized with COVID-19 in Royal Prince Alfred Hospital (RPA Hospital) in 2020 in relation to venous thromboembolic events (VTE), disseminated intravascular coagulation and outcome.

Method: We retrospectively collected clinical and laboratory data from hospitalised patients with confirmed COVID-19 in RPA Hospital from Feb 2020-Feb 2021. Patients were classified into non-ICU and ICU groups. Outcome at 4 weeks was classified as partial recovery, full recovery and death. Laboratory data including full blood count, PT, aPTT, fibrinogen, D-dimers, CRP, liver/kidney fuction tests, collected weekly for 4 weeks. Clinical data included the radiological evidence of VTE and ventilation requirements. Quantitative variables were compared using the Mann-Whitney test and categorical variables using the chi-squared test between patients of different groups. Correlation study was by Pearson's coefficient. Data were analyzed using GraphPad Prizm.

Results: Of the 61 patients hospitalized for COVID19 in 2020, 21% were hospitalized in ICU (**Table 1**). The length of hospitalization was less than 2 weeks in 68% of patients and the mortality rate was 6.5%. VTE was diagnosed in 3 (5%) patients and DIC in 1 patient, which was significantly lower than reported in the literature. From the inflammatory markers, CRP was significantly elevated in the ICU group compared with the non-ICU groups ($p<0.0001$). Coagulation parameter APTT was significantly elevated in the ICU group ($p<0.0001$).

Conclusion: We present our 1-year experience with hospitalized patients with COVID19. Routine biomarkers CRP and APTT were associated with disease severity in our cohort and may assist in monitoring disease outcome in hospitalized COVID19 patients.

Table 1. Demographics and clinical characteristics of patients included in the study

Characteristic	Mild illness (n = 31)	Severe illness (n = 17)	Critical illness (n = 13)
Age, mean/median (range)	56.35 / 57 (18-89)	62.06 / 62 (25-85)	62.77 / 66 (36-84)
Male, %	51.6 (16)	70.6 (12)	76.9 (10)
Ethnicity			
- Caucasian	14	10	5
- Asian	16	7	7
- Other	1	0	1
Smoking status, yes	1	0	1
BMI			
- <30	5	1	3
- >30 (obesity)	7	11	7
- NA	19	5	3
Hospital length of stay			
- < 2 weeks	26	12	4
- 2-4 weeks	5	5	1
- >4 weeks	0	0	8
Mechanical ventilation	0	0	7
Thromboprophylaxis			
- Clexane	25	13	10
- Heparin	1	2	1
- Other	0	2	0
- NA	5	0	2
Confirmed VTE	0	0	3
DIC	0	0	1
Outcome			
- Full recovery	30	15	2
- Partial recovery	1	1	8
- Death	0	1	3

Mild illness: No oxygen supplementation, Severe illness: oxygen supplementation, Critical illness: ICU

11.12

Oestrogen-Responsive miR-365a-3p and miR-548aa Expression is Increased in Whole Blood From Females on Hormone Based Contraceptives and During Pregnancy

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Aim: High oestrogen levels are associated with increased risk of venous thromboembolism (VTE), however, precise mechanisms remain unclear. microRNAs (miRs) are implicated in disease progression and are detectable in blood, thus may be potential biomarkers for monitoring oestrogen-mediated VTE. This study determined the expression of three selected oestrogen-responsive miRs (miR-365a-3p, miR-548aa and miR-494-3p), and their respective coagulation factor targets, in cohorts with low or high oestrogen levels.

Method: Whole bloods in PAXgene RNA, citrate and EDTA plasma from healthy women without contraceptives (controls) (n=31), on hormone-based contraceptives (n=17), and during pregnancy and post-partum (n=15). Expression of miR-365a-3p, miR-548aa, and miR-494-3p was measured using RT-qPCR. A coagulation factor panel was assessed by ELISA, STA-R® analyser, and Ceveron® alpha thrombin generation assay. One-way ANOVA was used for statistical analysis.

Results: Compared to healthy controls, women on contraceptives and during pregnancy had increased expression of miR-365a-3p and miR-548aa (2-fold). Conversely, miR-494-3p expression remained unchanged. Tissue factor and factor VIII activity were increased by ~3.5-fold ($P<0.05$, contraceptive group) and ~2-fold ($P<0.05$, the third trimester), respectively, in those with high oestrogen levels. In contrast, total and free protein S decreased by ~30-80 % ($P<0.01$) in the same group. Moreover, total thrombin generation was ~1.4-fold higher in cohorts with high oestrogen levels ($P<0.005$), compared to controls.

Conclusion:
Females with high oestrogen levels had increased miR-365a-3p and miR-548aa expression, but not miR-494-3p. In *in vitro* models, oestrogen-mediated miR expression is different, suggesting oestrogen response may be tissue specific. Furthermore, increased tissue factor and factor VIII activity as well as decreased protein S may contribute toward the hypercoagulable state in those with high oestrogen levels. Taken together, this pilot data suggests oestrogen-responsive miR-365a-3p and miR-548aa may be potential biomarkers to identify the hypercoagulability in cohorts with high oestrogen levels, and warrants further investigation.

11.14

The platelet proteome in health and type-2 diabetes

Dr Freda Passam

Platelets are central to blood clotting in health and disease by their rapid response to stimuli, such as thrombin activation. Their activation induces the secretion of proteins that promote platelet aggregation and inflammation. However, detailed analysis of the secreted platelet proteome is hampered by platelets' tendency to pre-activate during their isolation and a lack of sensitive protocols for low abundance releasate analysis. Here we present a high sensitivity analysis of the platelet releasate proteome with the detection of >1,300 proteins, comparing resting to thrombin-treated platelets. This analysis includes complementary quantification of the platelet lysates identifying >3,800 proteins to provide anti-correlation analysis for the secreted proteins. Unbiased scanning for post-translational modifications within releasate proteins, highlighted O-glycosylation as being a major component. For the first time, we have detected O-fucosylation on previously uncharacterised sites (i.e. on the platelet protein multimerin-1). In a group of 37 patients with type 2 diabetes and 32 matched patients without diabetes, there was marked increase in the secretion of proteins involved in coagulation (i.e. von Willebrand factor) and inflammation (i.e. CCL5, CXCL3) comparing platelets isolated from patients with diabetes with patients without diabetes. Our platelet proteome resource allows identification of novel regulatory mechanisms for drug targeting to address errors in platelet function and thrombosis in cardiovascular disease.

12. Nurses Free Communications

12.01

Improvement in patient experience with successful implementation of a Velcade at Home program in patients with myeloma

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Aim: Traditionally subcutaneous Velcade is delivered in a day ward environment. To reduce hospital visits for our patients, we introduced a Velcade at Home program (VAH) consisting of two arms; self-injection and general practitioner (GP) delivery. Here we present data on the patient experience outcomes.

Method: A Self-Injection Assessment Questionnaire was developed for both GP and self-injection arms, adapted from a previously validated tool[1]. The questionnaire elicited respondents' feelings about GP administration or self-injection using a Likert scale format with free text questions used to evaluate time and cost burden. The questionnaire was completed each week during the first cycle in the chemotherapy day unit, prior to cycle 3 (after one full cycle in the community) and at the end of cycle 4. All data were analysed using descriptive statistics.

Results: The first 20 patients enrolled onto the VAH Program were consented to the study, with 19 completing the program (15 self-injection, 4 GP).

In the self-injection arm 46% (7/15) of patients felt anxious prior to their first dose, this decreased to 0/15 by the end of cycle 4. No participants had difficulty removing the cap, depressing the plunger or administering the injection after their first cycle of training. The time reported to complete the injection was shorter for the self-injection arm when compared to their previous injections at hospital (mean 6 minutes and 280 minutes respectively). Similarly, patients in the self-injection arm reported a reduction in the cost burden associated with attending hospital. Of those who responded, 5/7 reported no costs associated with VAH.

Conclusion: The VAH program has been very well received with patients appreciating the opportunity to regain some control over their treatment and the potential for significant benefit in time and costs. We have been able to share our resources with 7 sites in Australia and New Zealand to help in implementation of a similar program.

References:

- Keininger, D., Coteur, G. Assessment of self-injection experience in patients with rheumatoid arthritis: psychometric validation of the Self-Injection Assessment Questionnaire (SIAQ). Health Qual Life Outcomes 9, 2 (2011). https://doi.org/10.1186/1477-7525-9-2

12.02

How we set up a complete outpatient autologous stem cell transplant (COASCT) program.

Mrs Cathie Milton

Aim: To develop and implement a Complete Outpatient Autologous Stem Cell Transplant (COASCT) program at our facility.

Background: Our facility has maintained an early discharge program (D+1) for autologous stem cell transplant (ASCT) patients since March 2001. A retrospective review of this early discharge program and clinical upskilling of apheresis staff informed the development of the COASCT program.

Method: Clinician and hospital executive support for program was sort for the nurse led model of care for this program within set prescriptive eligibility criteria.

The development of a clinical pathway and associated clinical assessment and resource tools for ongoing assessment and management of COASCT program patients inclusive of a multi-disciplinary approach to care was completed prior to commencing program.

The program commenced November 2020.

Results: 4 patients have completed the COASCT program at time of abstract submission. .2 (n4) patients completed program without requiring an inpatient admission. 1(n 4) patient was admitted, D+7 for pain management of mucositis. 1 (n 4) patient admitted D+10, with rapid atrial fibrillation. Total hospital stay for all (4) COASCT patients was 10 days versus hospital allocated stay (LOS) of 72 days (10 v 72).

Conclusion: COASCT program provides a safe alternative treatment model option for a subset of ASCT patients with a significant decrease in inpatient bed days, though we acknowledge the small number of participants in the program to date.
The impact on apheresis unit and staff was significant with associated clinical and assessment tool development requirements and associated assessment tools. However the program was well received by both the apheresis staff and program participants.

12.03

Regional myeloma patient model of care: An Alfred Health and Gippsland collaboration

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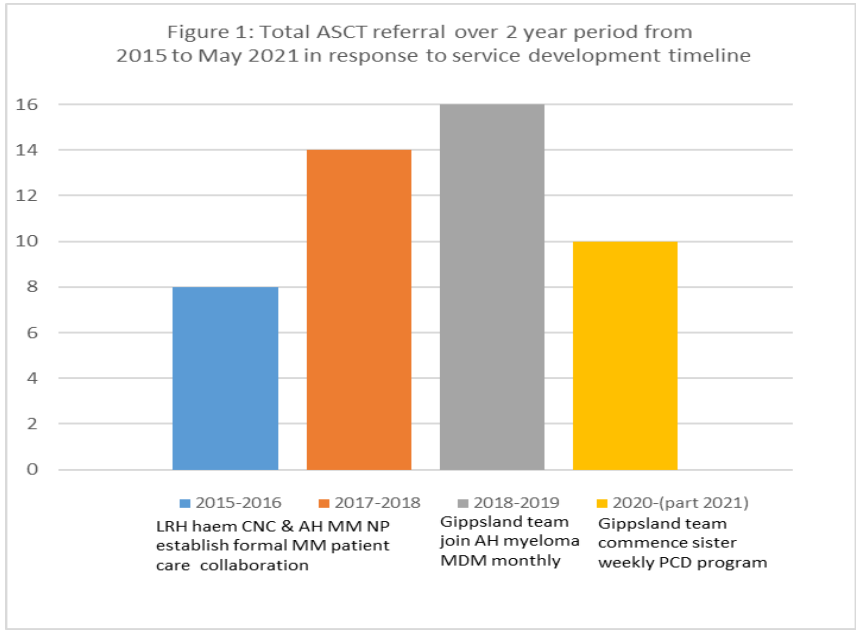
Aim: A key objective of The Victorian Cancer Plan 2021-2024[1] is the importance of health equity for Victorians so they are not disadvantaged by residence location. The complexity of care required for individuals with Multiple Myeloma (MM) highlights the need for novel approaches to achieve this objective. Alfred Health (AH) and Latrobe Regional Hospital (LRH) have developed a partnership providing regional MM patients' access to specialist tertiary advice and care.

Method: In 2015 a formal program of coordinated patient centred care for Gippsland MM patients began, led by the LRH haematology clinical nurse consultant and AH myeloma nurse practitioner. In 2018 the Gippsland haematology team joined the established AH MM multidisciplinary team meeting (MDM) on a monthly basis via zoom video conference. Gippsland regional patients diagnosed with MM are presented for consideration of Autologous Stem Cell Transplantation (ASCT), optimal choice of therapy and suitability for clinical trial entry. In 2020 LRH commenced a weekly sister PCD clinic, including supported telehealth appointments with AH and MDM participation.

Results:

Table one: Patient demographics referred for ASCT

	Male n (%)	Female n (%)
Number	32 (65%)	17 (35%)
Median age at diagnosis (yrs) [range]	65 [44-74]	64 [49-74]
Median age at ASCT (yrs) [range]	66 [44-75]	65 [50-74]



ASCT referrals from 2015 to April 2021 increased exponentially in response to service innovations timeline. The structured weekly sister program resulted in improvements in Gippsland's participation in the myeloma and related diseases registry (MRDR) and commencement of a MM regional trial program.

Conclusion: The development of a collaborative metro–regional model for a complex disease provides immediate access to specialist knowledge and decision making in a peer mentoring capacity as well as supported telehealth access for Gippsland MM patients. Improvements are demonstrated in referral numbers, expanding the delivery of quality care to regional patients and reducing the financial, emotional and transport toxicities compounding care. This model has provided a foundation for further improvements in patient centred care including PCD clinics throughout Gippsland as well as clinical trial enrolments for Gippsland MM patients in AH satellite sites.

1. Department of Health & Human Services Victorian Cancer Plan 2020-2024. Retrieved May 6, 2021 from https://www2.health.vic.gov.au/about/health-strategies/cancer-care/victorian-cancer-plan

12.04

Implementation and evaluation of a nurse-allied health clinic for patients after allogeneic haematopoietic stem cell transplantation

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Aim: Patients who undergo haematopoietic stem cell transplantation (HSCT) often have multiple health issues following discharge. In many centres, outpatient follow up is solely conducted by specialist physicians. We aimed to implement and describe the outcomes of a nurse-allied health multidisciplinary clinic.

Method: The clinic consisted of six disciplines - nursing, pharmacy, dietetics, physiotherapy, occupational therapy and social work. All allogeneic HSCT patients were reviewed at two weeks after discharge and on day 100 post allogeneic HSCT, with additional reviews as needed. Occasions of service, interventions, readmission data and physician satisfaction survey were collected prior to and after implementation. Additionally, patient feedback and quality of life survey (FACT-BMT) were collected during the first six months.

Results: From July to December 2019, 57 patients were reviewed in the clinic (475 reviews, average 8.3 reviews per patient). Common interventions included; nurse education (n=22), diet prescription (n=103), counselling by social worker (n=53), exercise programs by physiotherapist (n=111), medication lists provision (n=51) and fatigue management (n=43). The clinic did not reduce patients' readmission rate. The most common reasons for admission were fevers (38%), infection (14%), investigation and management of GVHD (23%) and cardiac/ renal/ respiratory issues (19%). These were beyond nursing and allied health scope to influence. Physicians survey demonstrated their increased satisfaction to nursing and allied health support to the patients, in particular emotional, functional and nutritional supports. Positive feedback from patients and carers were reported. FACT-BMT results demonstrated that there are unmet needs, particularly fatigue management, sexual education and support, body images, back to work support and quality of life improvement.

Conclusion: This clinic provides an innovative approach to patient-centred care. It has been well received by patients who were supported by multidisciplinary interventions.

12.05

Factors influencing attendance at and experiences of a long term follow up clinic post Allogeneic Bone Marrow Transplant for patients transitioning from paediatric to adult services.

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Aim: Explore and describe the facilitators and barriers to first attendance at an adult AlloBMT LTFU clinic in four cohorts of Adolescent and Young Adult (AYA) patients (18 years or older).

1. Identify the most common barriers and facilitators and utilise these to inform the future development of a toolkit for AYA's and staff to support transition from paediatric to adult AlloBMT LTFU services.

Method: The TransAllo study used a qualitative, interpretive methodology in order to gain knowledge about participant experiences of transitioning from paediatric to adult LTFU services.

Thirteen participants across 4 cohort consented to participate in audio-recorded semi-structured telephone interviews.

Results: Interpretive descriptive analysis of transcripts from semi structured interviews identified six key themes that participants from the four cohorts described from their own experiences of attending and transitioning from paediatric to adult LTFU post AlloBMT.

Conclusion: The TransAllo study used semi-structured telephone interviews to explore and describe facilitators and barriers to first attendance at an adult AlloBMT LTFU service by identifying commonly occurring factors.
All participants described feeling well supported by carers and health care providers in paediatric LTFU with carers coordinating attending appointments. They also described carers as being "keepers of knowledge" and their "story tellers" in terms of paediatric AlloBMT history. Participants recall emotions of anxiety and readiness to transition to adult LTFU. Participants overwhelmingly discussed the need for earlier and AYA-directed knowledge to prepare for transition, and earlier time to first appointment with the adult AlloBMT service. Given the additional responsibilities of personal commitments in adulthood, participants recommended more flexibility for adult LTFU appointments.

12.06

Unique requirements of genetic counselling in haematological malignancy disorders – experience from a genetic haematology service

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Aim: Somatic and germline genetic testing is now routine aspect of care for patients with genetic haematological disorders. Genetic counselling is important for facilitating informed consent and allowing for recommendation of management pathways. Whilst this has traditionally been provided within clinical genetics services/familial cancer centres, there is an increasing move for genetic counselling to be embedded within subspeciality areas. We sought to characterise the unique challenges arising in the care of patients with genetic haematological disorders and the implications for service delivery.

Method: Semi-structured interviews were conducted with nine patient/patient advocates regarding genetic counselling and management for patients with haematological disorders. Interviews were transcribed verbatim and coded using thematic analysis to identify major themes.

Results: Patient stakeholder interviews revealed that there can be difficulty in initially obtaining genetic diagnosis. Factors contributing included: novel and complex nature of their condition, clinician knowledge about genetic testing and limited access to genetic counselling services. Those participants who did receive a molecular diagnosis found it important to their clinical management and family planning discussions. Concern about the impact of a familial genetic cause of haematological malignancy on other family members, and their access to timely genetic counselling was also highlighted. This is particularly pertinent when family members are being considered as allogeneic stem cell transplant donors where there is a risk of transplant failure if a familial donor carries the same predisposing mutation.

Conclusion: Genetic counselling for haematological disorders presents unique issues and considerations. Genetic counselling has now been embedded within the Clinical Haematology service at Peter MacCallum Cancer Centre/Royal Melbourne Hospital. Multidisciplinary care is provided by clinical haematologists, genetic counsellors and clinical geneticists. These services can be successfully delivered from within a clinical haematology service with potential advantages given the specialised needs of this patient group.

12.07

Case study: a novel bispecific antibody treatment for multiple myeloma. Implications for nursing.

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Aim: Multiple myeloma (MM) is a rare, currently incurable plasma cell cancer which carries a high symptom burden and poor patient quality of life compared to other cancer groups. Bispecific antibodies are one of a group of novel immunotherapy agents currently under clinical investigation for the management of MM.

This case study aims to assist nurses in their understanding of these new agents and provide information on potential side-effects and the complexities of patient management.

Method: A case study approach will be used to identify the health care needs of a 59 year old patient with long-standing, aggressive MM who received this treatment at our facility. The presentation will outline the mechanisms of action of a plasma cell BCMA/T-cell CD3 targeted bispecific agent. Nursing care provided to the patient will be outlined and evaluated.

Results: The patient achieved a stringent complete response (sCR) at week 16. Drug and disease related side effects included cytokine release syndrome, neutropaenia and respiratory and gastrointestinal infections. Additionally our patient experienced issues including financial toxicity, agoraphobia secondary to diarrhoea and considerable fatigue which impacted quality of life to a degree which led her to consider withdrawing from the trial despite her excellent response. Collaboratively medical and nursing strategies were implemented to maximise patient outcomes.

The patient remains on trial in sustained sCR at week 152 and has returned to part-time work after long periods of non-employment due to ill-health.

Conclusion: Whilst these drugs offer potential to greatly improve disease outcomes, their toxicity profiles are complex and still evolving. Increased knowledge relating to these agents and their associated toxicities enhances the ability of nurses to meet the challenges in caring for patients receiving these agents.

12.08

Initial results of the NEPTUNE project: a Nurse-led outpatient follow-up program for Myeloma patients Treated with oral immune-modulatory drugs (IMiDS) at Eastern Health

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Aim: Patients on oral-only chemotherapy (OC) for myeloma (MM) typically have less nursing contact than those on subcutaneous or intravenous chemotherapy. This means less opportunity for nurse-initiated patient education.

We sought to audit patient medication compliance/understanding when treated with OC, followed by an intervention arm (NEPTUNE program) for OC patients of intensive nursing education to hopefully improve medication compliance/understanding, and treatment outcomes.

Method: We identified OC patients (lenalidomide/pomalidomide with dexamethasone +/- cycylophosphamide) between January 2018 and April 2020 through our Pharmacy database and medical records. Patients on clinical trials or thalidomide were excluded.

MM OC patients were offered phone-based nursing support. Our Myeloma Nurse undertook weekly calls for the first OC cycle, fortnightly for the second cycle. Participants completed a teaching tool for OC (MOATT), supportive care screen and quality-of-life questionnaire (EORTC QLQ-C30) at treatment commencement and at six-months.

Results: 121 OC patients were treated between Jan 2018 and April 2020. 44 patients were excluded, and 35/79 remaining patients were randomly selected for audit. Median age was 75 years, 26% were treated due to disease progression. 16 (46%) had incomplete compliance, and 27 (77%) experienced toxicity: 13 required treatment breaks, 11 dose reductions and 10 required blood transfusions.

Suboptimal compliance was as follows: No anticoagulation/aspirin in four patients (11%), no anti-viral in nine (26%), and no proton pump inhibitor with dexamethasone in six (17%).

Seven patients were recruited in two months for the intervention arm, five continue to treatment, one moved interstate, and one stopped treatment due to disease progression. Six patients experienced toxicity, three requiring emergency admission. Common toxicities were rash, pruritis, fever, ache, and fatigue.

Conclusion: There is a high rate of suboptimal compliance and toxicities with OC in MM. Patients on OC need additional support from nurses to improve medication understanding/compliance, and to manage toxicities appropriately.

12.09

To what extent do nurses consider body temperature to be a key indicator of neutropenic sepsis when initiating neutropenic sepsis protocols?

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Aim: Neutropenic sepsis is a life-threatening condition. Many clinical practice guidelines (CPG) for neutropenic sepsis management include a raised body temperature as a clinical indicator for initiating 'septic workup' protocols. However, not all septic patients present with a fever and patients with hypothermia have higher mortality rates than those with hyperthermia. This study was undertaken to investigate to what extent nurses consider body temperature to be an indicator of neutropenic sepsis for initiating neutropenic sepsis management protocols.

Method: The study used an explanatory sequential mixed methods approach. Data was collected from nurses recruited from the Haematology Society of Australia and New Zealand Nurses Group (HSANZNG) and the College of Emergency Nurses of Australia (CENA) in two phases. Phase one comprised of a Qualtrics survey covering:

- demographic data, knowledge and clinical experience
  - assessment of neutropenic patients
  - experience of neutropenic sepsis and CPGs/ protocols
  - influence of temperature as a clinical indicator.

Data collected from 125 respondents informed descriptive statistical comparison between the two cohorts (HSANZNG and CENA). This information, in turn, informed the questions for the Phase two: semi-structured interviews of a purposeful sample from 37 of the 125 respondents to the Qualtrics survey.

Results: Key differences between the cohorts related to their knowledge, experience and the perceived clarity of clinical practice guidelines and protocols. This paper presents the Phase one data.

Conclusion: Preliminary findings indicate differences in clinical practice between the two cohorts regarding the role of temperature in clinical assessment of neutropenic patients. The Phase 2 data is currently being analysed and it is hoped to provide meaningful insight into the phase1 findings.

12.10a

A real-world accuracy of oral mucositis grading in patients undergoing haematopoietic stem cell transplantation

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Aim: Oral mucositis is a common complication in patients undergoing haematopoietic stem cell transplantation. Accurate oral mucositis grading is essential for both clinical practice and oral mucositis research. This study aimed to evaluate the accuracy of daily oral mucositis grading by nurses in a tertiary hospital in Australia.

Method: A retrospective study was undertaken to review the daily patient oral assessment record, including diet, pain, erythema, ulceration and the oral mucositis grade based on World Health Organization (WHO) oral mucositis grading scale. The accuracy of the grade was determined by the observations recorded and reasons for inaccuracy was documented. Any repetition of the same error in the same patient was noted.

Results: In total, 6841 oral assessments in 373 patients, conducted between 2017 and 2020, were reviewed. A total of 70% (N=4781) were graded correctly. Of these 64% (N=3043) were grade 0. When the grade 0 scores were excluded, the accuracy of grading was reduced to 46% (N=1738). Common reasons for incorrect grading included; unable to grade due to diet not specified, no ulceration and no pain was scored grade 1, no ulceration was scored as grade 2-4, oral intake was not taken into account, and pain without ulcer was scored 0. A total of 77% of the errors were repeated in the same patient on consecutive days.

Conclusion: Our results suggest there is frequent inaccurate evaluation of oral mucositis and a need for nurse training to accurately assess oral mucositis.

12.10b

Improving the accuracy of oral mucositis grading: The impact of nursing education

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Aim: Oral mucositis is a common complication in haematopoietic stem cell transplantation (HSCT). It needs to be accurately assessed in daily practice and mucositis research. A previous audit showed frequent inaccuracy in nurse grading of oral mucositis using the World Health Organisation (WHO) mucositis scale. This project aimed to improve the accuracy through nursing education and describe the outcomes.

Method: It was a quality improvement project to improve oral assessment accuracy. An oral mucositis assessment manual was developed, a patient education brochure was created to encourage patient involvement, and nursing education was conducted. Pre-and post-education competency was evaluated with an 11-item online quiz, that included nurses' confidence in oral assessment, basic knowledge on how to conduct oral assessment, and seven case studies. The improvement was assessed using the student t-test.

Results: In total, 52 (pre-education) and 49 (post-education) nurses completed the quiz. Overall scores improved from 65% to 75%. After education, nursing confidence increased (79% vs 90%, NS) and influence by seeing previous assessments was reduced (37% vs 16%, p=0.03). Most of the nurses knew when to conduct oral assessments and when to cease assessments (correct answer given 88-100%). Accuracy of mucositis grading for the case studies improved from 54% to 66% (significant in two cases). Low scores were noted when patient's oral intake was affected without ulceration (grade 1).

Conclusion: Nursing education improved nurses' confidence in oral assessment and their knowledge to grade oral mucositis. However, post-education scores, particularly for accurate grading in the case studies was still 66% suggesting the need for continuous education and evaluation.

12.11

The caregiver experience of haematopoietic stem cell transplant (HSCT) for haematological malignancy in the provincial New Zealand setting (2019).

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Aim: To explore the experience of haematopoietic stem cell transplant (HSCT) from the perspective of the caregiver within the provincial New Zealand setting.

Method: A qualitative descriptive study using interviews underpinned by a narrative inquiry methodological approach. A sample of eight HSCT caregivers were interviewed within the time period of six months to five years post-transplant. The interview data was examined, utilising both a narrative and thematic analysis approach.

Results: The study findings reveal the breadth of the caregiver journey and provide compelling insight into the depth of duty and responsibility HSCT caregivers perceive they have. The findings describe the practical, social and emotional impact which relocation exerts upon the lives of caregivers within the provincial New Zealand context. The transplant experience continues to influence the lives of caregivers across the HSCT trajectory during the weeks, months and years following transplant. The participants provided suggestions for how health care teams might best prepare and support future HSCT caregivers.

Conclusion: The study findings express a clear message for health services to increase their focus toward the provision of information and support strategies aimed specifically at HSCT caregivers. The study provides evidence based insight which can be used to inform the development of nursing interventions, and shape strategies across the multidisciplinary health care team, in order to provide health services which effectively address the needs of HSCT caregivers within the provincial New Zealand setting. Although the study focus is specific to haematopoietic stem cell transplantation in New Zealand, the findings provide compelling insight which may also be relevant to HSCT caregiver populations in other provincial geographical settings.

13. BMTSAA Free Communications

13.01

Do cryopreserved grafts impact outcomes following allogeneic stem cell transplant?

Dr Wei Xia[1,2,3], *Dr Lijun BAI[1,2,3], Sir Cassandra REID[1], Ms Kelly WONG[1], A/Professor William STEVENSON[1,3], Professor Chris WARD[1,3], Professor Ian KERRIDGE[1,3], Dr Luke COYLE[1], Dr Keith FAY[1], Dr Ashley MCEWAN[1], Dr Matthew GREENWOOD[1,3]*

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Aim: As a result of travel restrictions associated with the COVID-19 pandemic, donor stem cells (HSC) from other centres/states/countries could not be transported fresh for allogeneic stem cell transplant (allo-HCT) and were cryopreserved at hubs prior to transport. We aimed to assess whether routine cryopreservation of HSC impacted outcomes of allo-HCT at our centre.

Methods: From 01/2016 till 3/2021, patients who underwent allo-HCT at our site who received fresh HSC product (cohort A) or cryopreserved HSC product (cohort B) were retrospectively assessed for allo-HCT outcomes. Donor source, recipient age, gender, infused CD34/CD3 doses, and allo-HCT outcomes were compared between cohort A and B.

Results: For the entire cohort, median age at transplant was 56.5 (19-73) yrs. 55.9% were male. Median follow-up was 589 (3-1842) days. Donors were related (n=50), unrelated (n=113), haploidentical (n=7). Cohort A consisted of n=133 allo-SCT recipients, cohort B, n=37. There were no significant differences in recipient age, gender or donor source between cohorts. Cohort B received more CD34 (6.5$\pm$1.83 vs 5.1$\pm$1.02 x10^6/kg, p=0.002); and more CD3 (2.5$\pm$1.13 vs 2.1$\pm$1.06 x10^8/kg, p=0.028). Cohort B experienced significant delays in platelet engraftment at the count of 20 x10^9/L (24$\pm$6.38 vs 20$\pm$7.03 days, p=0.037), 50 x10^9/L (25$\pm$9.83 vs 20$\pm$6.50 days, p=0.011) and 100 x10^9/L (31$\pm$17.55 vs 21$\pm$9.87 days, p=0.001). There were no differences in time to neutrophil engraftment, chimerism, aGVHD, TRM, relapse rate or survival between cohorts.

Conclusion: In our centre, allo-SCT using cryopreserved HSC was associated with delayed platelet engraftment but otherwise acceptable post allo-HCT outcomes.

Reference:

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13.02

Cryopreserved unrelated donor haemopoietic progenitor cell (HPC) products during COVID-19: a retrospective single centre review

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Aim: Since April 2020, all matched unrelated donor (MUD) HPC, Apheresis (HPC, A) products have been received as cryopreserved products in Australian transplant centres (TC) due to COVID-19. The products are processed and cryopreserved at donor centre or central processing laboratories and are shipped unaccompanied in dry shippers to TC. Previously MUD HPC,A was transported fresh over 18-72 hrs and infused fresh at the TC. We aim to contribute to understanding the characteristics, safety and quality of this new transplant model.

Method: To date, our transplant laboratory has received a total of 29 cryopreserved MUD HPC,A products. CD34 post thaw recovery was calculated as the CD34 cell count post thaw divided by the fresh CD34 cell count. CD34 doses per kilogram of recipient weight were reviewed. Additionally, we have reviewed clinical data after transplant up to day 100 and compared to the previous two years of fresh MUD HPC, A transplant data. Excel Analyse-IT was used for statistical analysis.

Results: We received products processed at 10 different centres in 5 different countries. The median post thaw CD34 recovery was 71% (21% - 105%). We found that 3 products had a recovery of < 50%. Of the 26 mobilisations, a fresh dose of CD34 >5x10^6/kg was achieved in 21 mobilisations (81%) and of these 90% had a post thaw CD34 dose > 3 x10^6/kg. Of the 4 mobilisations with fresh doses < 5x10^6/kg, only 1 subsequently returned a post thaw CD34 dose of >3x10^6/kg. Similar to other reports (personal communication) we did encounter a variety of quality related problems with some of the products. Engraftment outcomes are being collated.

Conclusion: The need for cryopreserved donor products is likely to continue for some time yet. Our experience indicates that on average quality is acceptable but there is scope for improvement and further monitoring of long term graft outcomes is needed.

13.03

Meeting the COVID challenge: optimizing viable CD34+ enumeration in cryopreserved HPC samples for implementation of an external QA Program.

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Aim: The COVID-19 pandemic forced a fundamental change in the global procurement of allogeneic hematopoietic progenitor cells (HPC) for transplantation. To better meet the emergent challenges of transporting cryopreserved allogeneic HPC, there is an urgent need for external Quality Assurance Programs (QAPs) to evaluate reproducibility and harmonization of viable $CD34^+$ HPC ($vCD34^+$) enumeration as the current external QAP is unsuitable for analysis of $vCD34^+$. The cost-effective distribution of HPC cryopreserved reference samples (CRS) with acceptable reproducibility is key to a successful external $vCD34^+$ QAP program.

Method: Cryopreserved HPC samples were either stored on dry ice for 1-4 days, or on dry ice for one day followed by liquid nitrogen (LN_2) storage for 1-3 days to assess optimal conditions for $vCD34^+$ QAP. Flow cytometric enumeration of $vCD34^+$ HPC was performed utilizing a single platform assay combined with 7-AAD viability dye exclusion. The optimum transportation condition was validated in pilot and multi-center (n=12) national studies which involved transport of CRS on dry ice to recipient centers followed by LN_2 storage.

Results: A combination of one day on dry ice followed by LN_2 storage stabilized the viability compared to continuous storage on dry ice. For the national multicenter study, transportation distances ranged from 0.5 - 4,000 km (median 513 km) with transit times ranging from 1- 26 hours (median 22.5 hours).

Overall, 8/12 centers (67%) returned comparable results that were within ±10% of the median. There was no significant difference between samples tested immediately upon arrival or after subsequent LN_2 storage ($p=0.41$). There was no significant relationship between comparability of $vCD34^+$ counts and i) sample transit time ($R=0.67$, $p=0.07$) nor ii) distance travelled ($R = 0.19$, $p=0.55$), demonstrating that laboratory outcome was unlikely to be related to sample transport.

Conclusion: Dry ice distribution of cryopreserved HPC for up to 26 hours results in a stable CRS that can enable the commencement of external QAP programs for $vCD34^+$ HPC enumeration. The estimated cost of safer and more convenient dry ice delivery is >20-fold lower than LN_2

H001 – H185: HSANZ Posters

H001

D-Dimer cut off for APML; complementing morphology for early diagnosis and ATRA initiation

Dr Michael Ashby[1], *A/Prof Jake Shortt*[1], *Prof Stephen Opat*[1], *Dr Anastasios Nalpantidis*[1], *Dr George Grigoriadis*[1], *Dr Michael Low*[1], *Dr Pasquale Fedele*[1], *Dr Susan Brown*[1], *A/Prof Sanjeev Chunilal*[1]
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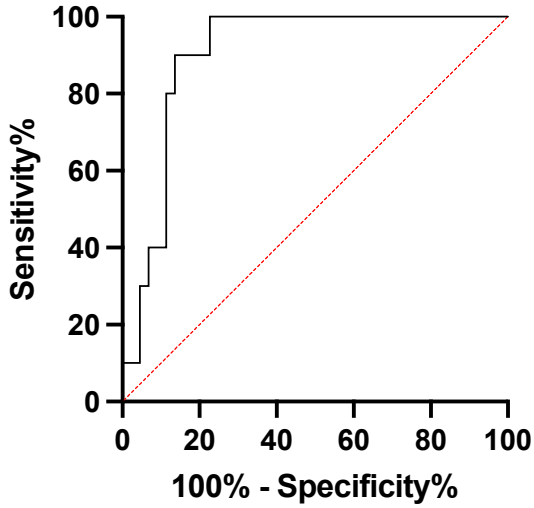
Aim: Acute promyelocytic leukaemia (APML) is suspected on characteristic morphological and clinical features prompting immediate treatment with all-trans retinoic acid (ATRA). Often associated with a degree of disseminated intravascular coagulopathy, we aimed to determine if a d-dimer cut-off value can assist in predicting APML versus acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL) for early emergency treatment.

Method: Retrospective review of patients with acute leukaemia presenting to a tertiary metropolitan centre from Aug 2018 – Feb 2021 with a D-Dimer collected prior to any treatment. Patients were diagnosed according to WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition, 2017, and APML confirmed by molecular cytogenetic evidence of *PML-RARa* fusion. D-dimer levels were measured using a latex microparticle turbidometric analyser using the ACL TOP for all patients at presentation, and a receiver-operator curve was created.

Figure 1: D-Dimer for prediction of APML



Results: 54 patients were included: 10 APML, 39 AML, 4 B-ALL and 1 T-ALL with a median age of 54 years (range 18 - 89). All APML patients had molecular evidence of *PML-RARa* fusion. Median D-Dimer for APML was 3.72 (range 1.52 – 70), and 0.36 (range 0.04 – 64) for the non-APML group. Area under the curve was 0.90, 95% CI 0.8214 – 0.9831, p<0.0001 (Figure 1). Using our analyser, a D-Dimer value of 1.44 correlated with a sensitivity of 100% and specificity of 77%. Negative predictive value was 100% at this cut off. The non-APML patients with D-Dimer >1.44 consisted of 8 AML and 1 ALL, they had higher median white cell count than those with low D-dimer (12.4 x 10^9/L, range 0.7-430 vs 2.74, range 0.5-88).

Conclusion: At our centre, a d-dimer of <1.44 reliably excluded APML. In addition to careful morphological examination, this may complement emergency decision making for management of APML. Further studies are needed to confirm this observation.

H002

Next generation sequencing in newly diagnosed acute myeloid leukaemia: a real world experience of the impact on patient management

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Aim: Next Generation Sequencing (NGS) has enabled extensive sequencing of Acute Myeloid Leukaemia (AML) and has broadened our understanding of the genetic changes driving leukaemogenesis. This has led to changes in the classification, prognostic stratification, treatment and response assessment of AML. Here we share our experience of establishing a myeloid NGS panel (AMLGP) and performing diagnostic sequencing on patients presenting with AML in the Auckland City region.

Method: 101 consecutive AML patients were prospectively enrolled from January 2019 until December 2020. A capture based gene panel including all the coding exons of 78 genes commonly mutated in myeloid malignancies was designed and diagnostic samples were sequenced to a depth 200x mean target coverage on an Illumina NextSeq500 machine. Somatic variants were detected and curated with a custom bioinformatics pipeline.

Results: Of the 101 patients studied, 95 had a somatic mutation in one or more genes. The number of mutations detected in each sample ranged from 1-14 (median 3.36). Our AMLGP detected a molecular lesion in all AML cases with a normal karyotype (n=47) and allowed us to risk stratify 32.7% of cases more precisely by utilising a genomic classification of AML. 30.7% changed from intermediate to poor risk and 2% changed from intermediate to favourable risk. An NGS marker suitable for Minimal Residual Disease (MRD) assessment was detected in 95% of cases and 53.5% of patients had at least one druggable target. Surprisingly, this study revealed 4 cases with familial *DDX41* mutations and one case with a germline *CEBPA* mutation.

Conclusion: When used as part of the diagnostic work up of AML, the AMLGP meaningfully altered the classification, risk stratification, management and assessment of treatment response in a substantial proportion of newly diagnosed AML. The finding of a high prevalence of familial cases of AML was unexpected, and has considerable implications for management.

H003

Association of BAALC expression with genetic mutations in cytogenetically normal acute myeloid leukemia in adult patients

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Introduction: Acute myeloid leukemia (AML), a cytogenetically and molecularly heterogeneous disease, constitutes approximately 35% of adult leukemia. Karyotype at the time of diagnosis has been traditionally used in the risk stratification of adults with AML. However, 40 to 50% of AML patients do not have clonal chromosomal aberrations. This karyotypically normal group, CN-AML, less well understood biologically and clinically, has been shown to have genetic mutations and altered gene expression that predict prognosis. *BAALC* gene has been identified as a leukemia-associated gene and has been shown to be associated with poor patient outcome. NPM1, FLT3-ITD and CEBPA mutations have been incorporated by European leukemianet, 2016 in the risk stratification of AML patients.

Aims: The aim of this study was to investigate the association of genetic mutations with BAALC expression in CN-AML adult patients.

Method: In this prospective study, 149 CN-AML adult patients were recruited. We determined the expression of BAALC gene at diagnosis and examined its correlation with genetic mutations- NPM1. FLT3-ITD and CEBPA and patient outcome.

Results: *BAALC* gene was overexpressed in 60 (40.27%) CN-AML patients. We did not find any association between BAALC expression and age at diagnosis (p=0.37), gender (p=0.16), total leucocyte count at diagnosis (p=0.12). The BAALC overexpression was associated with NPM1 wild type status (<0.001). However, it was not associated with FLT3-ITD (p=0.198) and CEBPA mutations (p=0.85). CEBPA-NPM1+FLT3- patients had lower *BAALC* expression as compared to CEBPA-NPM1-FLT3+ (p=0.0028) and CEBPA-NPM1-FLT3+ (p<0.001) (Fige 1).
On survival analysis, we found a significant association between BAALC expression and overall survival (OS) (p=0.017). However, we did not find any association between its expression and event free survival (p=0.49). On further analysis of FLT3-ITD$^-$/NPM1$^-$ double negative CN-AML patients, we found BAALC overexpression still predicted poor OS (p=0.02).

Conclusion: We conclude that BAALC expression is low in CEBPA-NPM1+FLT3-. BAALC expression is associated with poor OS. The testing of its expression can be used to risk stratify CN-AML patients, particularly, FLT3-ITD$^-$/NPM1$^-$ double negative patients in routine clinical practice.

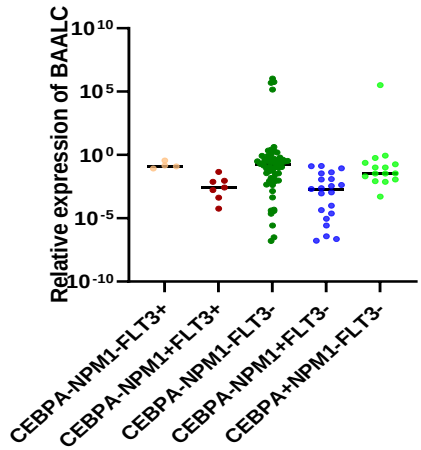

Figure 1. Association of genetic mutations (NPM1, FLT3-ITD and CEBPA) with *BAALC* expression

H004

Treatment free remission (TFR) after ceasing venetoclax-based therapy in patients with acute myloid leukemia

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Aim: Ph3 studies confirmed the benefit of adding venetoclax (VEN) to hypomethylating agents (HMA) or low-dose cytarabine (LDAC) in older/unfit pts with newly diagnosed AML with a median duration of response of 12-18 months (mo). It is currently unknown whether pts should continue therapy until progression and whether elective therapy cessation could detrimentally impact outcomes.

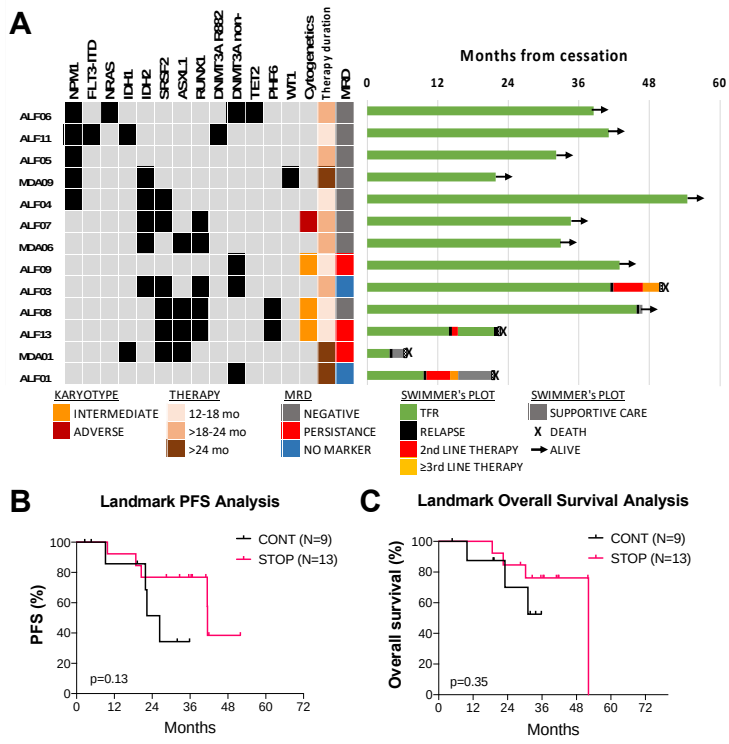
Method: Retrospective analysis of pts with AML receiving VEN plus either HMA or LDAC for 12mo and in first remission. Two treatment approaches were compared: elective cessation of therapy in remission followed by monitoring (STOP) or continued therapy until relapse (CONT).

Results: 25 pts were included from 3 institutions: 13 in STOP and 12 in CONT. The median follow-up was 55mo. Treatments included VEN-HMA (68%) or VEN-LDAC (32%). The median number of cycles received was shorter in STOP (17; range 12-29) vs CONT (30; range 12-57). Median time on therapy (TOT) was shorter in STOP (19.1mo vs 33.2mo). In STOP, the reason for treatment cessation was patient request (46%) and medical (54%), with a median treatment-free remission (TFR) of 45.8m (Figure 1A). 2/5 relapses occurred >36mo of TFR. In CONT, 8(67%) have relapsed, with 5 relapsing >24mo of therapy. More pts had acquisition of cytogenetic abnormalities at relapse in CONT (6/8; 75% vs 2/5; 40%).

14 had *NPM1* and/or *IDH2* mutations. 10 achieved undetectable MRD (by flow and/or qPCR), of which 1 relapsed. In STOP, 7/8 with *NPM1* and/or *IDH2* mut are still in TFR. A landmark analysis was performed which revealed no significant difference in progression free (p=0.13) or overall survival (p=0.35) in STOP vs CONT cohorts (Figure 1B-C).

Conclusion: In elderly/unfit pts with AML receiving front line VEN-based treatment and in CR/CRi >12 months therapy, the likelihood of a durable TFR is highest among pts with *NPM1*/*IDH2* mutation and MRD negativity at therapy cessation.

Figure 1



H005

Jumping translocation involving chromosome 13q in a patient with Crohn's Disease and inv(16)(p13.1q22)/CBFB-MYH11 Acute Myeloid Leukaemia

Ms Sarah Clarke[1], *Ms Rebecca De Kraa[1], Dr Katherine Creeper[2], Prof Michael Leahy[2], Dr Matthew Wright[3]*
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Jumping translocations (JT) are rare chromosomal rearrangements caused by the translocation of the same fragment of chromosomal material to two or more recipient chromosomes, resulting in multiple related clones.[1] In the setting of myeloid neoplasms, JT are typically associated with disease transformation to acute myeloid leukaemia (AML), and studies to date have found JT to be associated with poor prognosis and short overall survival.[2] However, JT are rarely reported in de novo AML, and even less frequently found to be associated with a favourable AML prognostic cytogenetic marker.[3,4] Additionally, JT have rarely been described in haematological malignancies associated with autoimmune diseases such as Crohn's Disease (CD).[5] Here we describe a case of inv(16)(p13.1q22)/CBFB-MYH11 AML in a 40-year-old female with a 24-year history of CD treated with the immunosuppressive drug Azathioprine. Cytogenetic analysis at diagnosis of AML demonstrated the inv(16)(p13.1q22) rearrangement in conjunction with sideline clones containing trisomy 13, tetrasomy 13, and a JT of chromosome 13q12 jumping to 7q32 and 18p11.2. The patient attained molecular remission one month post diagnosis after induction 7+3 chemotherapy. Morphologic relapse of disease occurred 27 months post diagnosis. A second molecular remission was attained 3 months post morphologic relapse after re-induction chemotherapy. Thirty-two months post diagnosis the patient was transplanted with a sibling bone marrow allograft and is currently in remission 2 months post-transplant. To the best of our knowledge, this case represents the first report of JT occurring in inv(16)(p13.1q22)/CBFB-MYH11 AML and the second of JT occurring in an AML patient with prior clinical history of CD. This case provides further insight into the rare occurrence of JT in de novo AML, in particular AML with a favourable cytogenetic marker in conjunction with autoimmune disease.

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H006

A phase 1 study of gilteritinib in combination with induction and consolidation chemotherapy in patients with newly diagnosed AML: final results update

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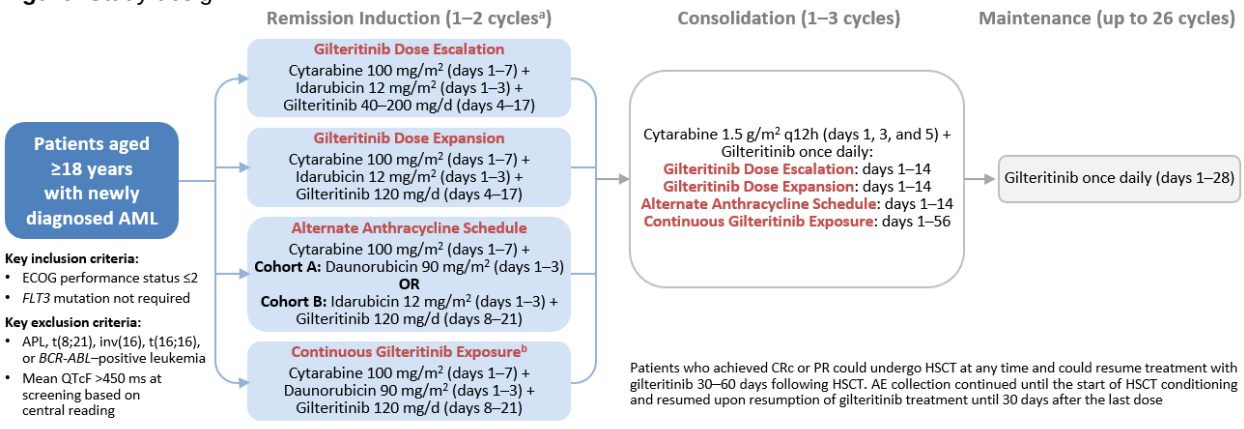
Aim: We report updated final data from a phase 1 study of once-daily gilteritinib, an oral FMS-like tyrosine kinase 3 (FLT3) inhibitor, plus intravenous chemotherapy in patients with newly diagnosed (ND) acute myeloid leukemia (AML).

Methods: As detailed in Pratz et al. *Blood* 2020;136(suppl 1):16–17, this 4-part, open-label, study (NCT02236013) assessed safety/tolerability and antileukemic effects of gilteritinib plus 7+3 induction and ≤3 cycles of high-dose cytarabine consolidation, and as single-agent maintenance treatment in adults with ND AML (**Figure**).

Results: As of 23 June 2020, 80 patients were allocated to treatment (safety analysis set, n=79); 44 were *FLT3* mutation–positive (*FLT3*$^{mut+}$). Median follow-up was 35.8 months. Hematopoietic stem cell transplantation was performed in 24/79 (30.4%) patients. Dose-limiting toxicities occurred in 15/79 (19.0%) patients. Maximum tolerated dose was 120 mg/d. Serious treatment-related adverse events and adverse events leading to gilteritinib discontinuation occurred in 23/79 (29.1%) and 18/79 (22.8%) patients, respectively. A gilteritinib 120-mg/d dose was received by 38/44 (86.4%) *FLT3*$^{mut+}$ patients. In Pratz *Blood* 2020, we reported clinical responses at end-of-induction but now report response at end-of-treatment, consistent with previous disclosures. Among *FLT3*$^{mut+}$ patients who received gilteritinib 120 mg/d, composite complete remission (CRc) rate was 89.5% (complete remission [CR], 71.1%; CR with incomplete hematologic recovery, 18.4%) and median overall survival has not been reached. Estimated 1- and 2-year survival probabilities were 85.9% and 72.3%, respectively. The 60-day mortality rate was 0%. Median (95% confidence interval) disease-free survival was 13.3 (4.9–18.7) months. In patients who received gilteritinib 120 mg/d and achieved CRc, mutational clearance of *FLT3* internal tandem duplication (ITD) (summed *FLT3* ITD:wildtype signal ratio of ≤10^{-4}) after induction or consolidation was 84.6% (11/13).

Conclusions: Gilteritinib plus induction and consolidation chemotherapy is well tolerated in patients with *FLT3*$^{mut+}$ ND AML and leads to CR, clearance of *FLT3* ITD, and long-term survival.

Figure. Study design.



[a]If day 21 bone marrow evaluation shows residual blasts and the bone marrow is not aplastic, a second induction cycle with the same regimen could be started ≥7 days after the last dose of gilteritinib but no later than day 28 (gilteritinib dose-escalation and dose-expansion cohorts) or day 35 (alternate anthracycline schedule and continuous gilteritinib exposure cohorts) of the first induction cycle; [b]During the second induction cycle, the dosage of daunorubicin was reduced to 45 mg/m².
AE, adverse event; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; *BCR-ABL*, breakpoint cluster region-Abelson murine leukemia viral oncogene homolog; CRc, composite complete remission; ECOG, Eastern Cooperative Oncology Group; *FLT3*, FMS-like tyrosine kinase 3; HSCT, hematopoietic stem cell transplantation; PR, partial remission; q12h, every 12 hours; QTcF, Fridericia-corrected QT interval.

H007

FLT3 mutations in Australian AML patients (FLAME) – an analysis of FLT3 testing, mutational prevalence and clinical outcomes

Dr Genevieve Douglas[1], *Wendi Lin*[1], *Dr Sun Loo*[2], *Dr ZhiHan Yeoh*[3], *Dr Rishu Agarwal*[1], *Dr Ashish Bajel*[3], *Prof Andrew Wei*[2], *Maha Cooney*[4], *Dr Chun Yew Fong*[1]

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Aim: Novel therapeutic agents have changed the therapeutic paradigm in acute myeloid leukaemia (AML). Agents targeting aberrant Fms-like tyrosine kinase (FLT3) activity are now standard of care in upfront and maintenance settings and increasingly available for relapsed/refractory patients. Appropriate selection of and access to these therapies is dependent upon the quality and consistency of timely FLT3 mutation testing. Furthermore, FLT3 mutational status may evolve throughout the disease continuum, and acquisition may be a driver for therapeutic resistance. There is no harmonised approach to FLT3 testing in Australia. We aim to illustrate FLT3 mutational prevalence in an Australian cohort, along with testing characteristics such as turnaround time, and impact of FLT3 status on therapeutic decisions.

Method: A retrospective analysis of FLT3 testing performed over a 24-month period in AML patients (April 2018 – April 2020) at Austin Health, Alfred Health and Peter MacCallum Cancer Centre has been undertaken. FLT3 mutation prevalence, consistency of intra- and inter-laboratory turnaround times, patient access to targeted therapies and frequency of acquisition/loss of FLT3 mutation at relapse in this cohort has been determined.

Results: Australian FLT3 mutation prevalence approximates previously reported rates (30%). FLT3 inhibitors were used almost uniformly in mutated patients upfront, with testing turnaround times ranging from 2-8 days, adequate for addition of midostaurin at day 8. In relapsed/refractory AML, an inconsistent approach to FLT3 testing was observed. Use of FLT3 inhibitors in this setting was variable.

Conclusion: Assessment of FLT3 mutational status in AML patients confers significant prognostic and therapeutic value. Effective implementation of novel therapies requires robust testing infrastructure and improvement in testing turnaround times. Repeat testing in patients with relapsed/refractory AML is essential for appropriate access to second-generation inhibitors, and should be considered in all patients. Our data identify areas for improvement and may assist implementation of new therapeutic approaches into this increasingly complex paradigm.

H008

Real-World Treatment Patterns and Clinical Outcomes in Unfit Patients with AML Receiving First-Line Systemic Treatment or Best Supportive Care (CURRENT): Australian Specific Dataset

Assoc Prof Anoop Enjeti[1], *Dr Duncan Purtill*[2], *Associate Professor Stephen Ting*[3], *Associate Professor Emily Blyth*[4], *Mr Yinghui Duan*[6], *Dr Alex Delgado*[5], *Ms Belen Garbayo Guijarro*[7], *Dr Carolyn McNees*[8], *Dr Andrew Birchley*[9]

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Aim: To evaluate real-world clinical outcomes in patients with AML deemed unfit for intensive chemotherapy (IC) receiving first-line therapy or best supportive care (BSC).

Method: Australian-specific data from a global retrospective chart review across 112 centres in 22 countries is reported. Adults with primary or secondary AML deemed unfit for induction IC receiving first-line low-intensity chemotherapy, targeted therapy, or BSC between 1 January, 2015, and 31 December, 2018 were included. The primary endpoint was overall survival (OS) from diagnosis of AML. Secondary endpoints included progression-free survival (PFS), time to treatment failure, and response rates (complete response [CR] + CR with incomplete hematologic recovery [CRi]) per treating physician's assessment.

Results: The final data cutoff on 31 March, 2020 included 138 patients (from 5 centres), of whom 75 (54%) received first-line systemic therapy and 63 (46%) received BSC. Of those receiving first-line therapy, 32 (42.7%) received azacitidine (AZA) monotherapy, 14 (18.7%) received low-dose cytarabine (LDAC) monotherapy, 29 (38.7%) received other systemic therapies, including combinations. Median OS was 4.0 months in the total population and 7.5 months in those who received systemic therapy, including 10.0, 5.0, and 5.0 months for patients who received AZA, LDAC, and other systemic therapies, respectively, and 2.5 months for patients who received BSC only. Median PFS was 8.6, 2.8, 4.4, and 2.1 months in patients who received AZA, LDAC, other systemic therapies, and BSC only, respectively. CR+CRi was achieved by 16% of patients who received first-line systemic therapy.

Conclusions: Clinical outcomes for AML patients unfit for IC in Australia remain poor. OS for AZA, LDAC, and BSC was consistent with clinical trials, with median OS <10 months for all treatment options. Nearly half of patients received BSC only, with AZA and LDAC being common treatment choices. Development of effective therapies remains an unmet clinical need in AML patients unfit for IC.

H009

Blinatumomab with chemotherapy is effective in inducing minimal residual disease (MRD) negative remissions in up-front treatment of adults with B-precursor Acute Lymphoblastic Leukaemia (ALL) – results from the ALLG-ALL08 study

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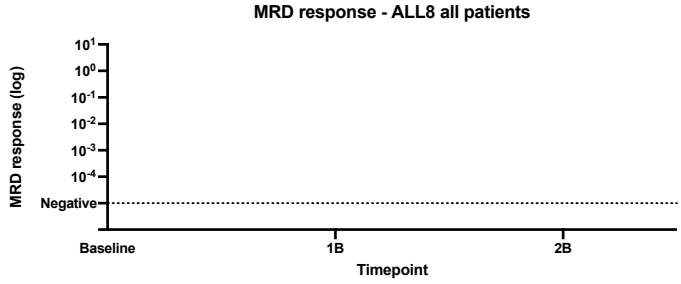
Aim: To evaluate the rate of MRD negative remission in adult patients receiving Blinatumomab in combination with chemotherapy as part of the Australasian Leukaemia & Lymphoma Group (ALLG) ALL08 study.

Method: The ALLG08 study evaluated Blinatumomab following a low-intensity debulking phase of chemotherapy followed in alternating cycles with methotrexate and cytarabine for central nervous system prophylaxis. 30 patients aged 40 – 65 years were enrolled in centres across Australia. PCR MRD analysis was performed on bone marrow samples to detect *IG/TCR* rearrangements at a central laboratory for timepoints following cycle 1B, 2B and 4B. Patients then proceeded to 24 months of maintenance therapy. This analysis is based upon the MRD response data following cycle 1B and 2B.

Results: Of 30 patients enrolled on study, 27 patients (90%) attained either CR (26) or CRi (1) with 1 patient refractory and 2 unevaluable. The single refractory patient attained CR at the end of cycle 2B. 27 patients had suitable MRD markers with 26 tested for MRD post 1B and 24 tested post 2B. At the end of cycle 1B, 15 patients (55%) had attained an MRD negative response, with a further 4 (15%) having an MRD level of 10^{-4} or less for an overall MRD response rate of 70%. By cycle 2B, 18 were MRD negative (75%) with a further 2 having MRD of 10^{-4} or less (8%) for an MRD response rate of 83%. Of those MRD positive at 1B, 5 patients converted to MRD negative by 2B with 1 patient losing an MRD negative response by timepoint 2B.

Conclusion: Reduced intensity chemotherapy in combination with blinatumomab has a high morphological and minimal residual disease response rate in adults with B-ALL. The majority of responses are early with some deepening of responses by 2B.



H010

CD44 and its ligand osteopontin are upregulated in KMT2A-AFF1 T-cell acute lymphoblastic leukaemia

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Aim: T-cell acute lymphoblastic leukaemia (T-ALL) is associated with heterogeneous genomic abnormalities, including *KMT2A*-rearrangements (*KMT2A*r), *MLLT10*-rearrangements (*MLLT10*r) and the *NRAS*^{G12D} mutation. Changes in proliferation, surface markers and gene expression were interrogated in cell lines harbouring these abnormalities to elucidate the molecular mechanisms of T-ALL. These results will inform development of targeted therapeutic approaches, to improve patient outcomes.

Method: *KMT2A-AFF1, PICALM-MLLT10, DDX3X-MLLT10* and *NRAS*^{G12D} were cloned and expressed in murine CD4^{+}CD8^{+} MOHITO cells. *KMT2A-AFF1* was expressed in murine Ba/F3 cells, as a B-cell ALL (B-ALL) comparator. RT-PCR and Sanger sequencing confirmed expression of transduced constructs. CellTiter-Glo was used to assess proliferation, qRT-PCR for molecular targets, and flow cytometry for surface markers. Statistical significance was assessed by unpaired t-tests.

Results: Expression of *KMT2A-AFF1* or *NRAS*^{G12D} in MOHITO cells significantly increased cell proliferation compared to parental cells (p=0.001 and 0.0001, respectively). CD44 was upregulated in *KMT2A-AFF1* and *NRAS*^{G12D} MOHITO cells, compared with negligible expression in parental cells (p=0.04 and <0.01, respectively). Upregulation of the CD44 ligand osteopontin (*OPN*) occurred only in *KMT2A-AFF1* MOHITO cells (p=0.005, compared to parental). Expression of *DDX3X-MLLT10* or *PICALM-MLLT10* in MOHITO cells, or *KMT2A-AFF1* in Ba/F3 cells, did not induce alterations in *OPN* or CD44 expression, or cell proliferation.

Conclusion: This study is the first evidence of a role for *OPN* in the molecular mechanisms of *KMT2A*r T-ALL. We generated *in vitro* models of several T-ALL genomic subtypes, and identified that CD44 is expressed in *NRAS*^{G12D} and *KMT2A*r T-ALL, but not in *MLLT10*r cell lines. *OPN* upregulation occurred only in *KMT2A*r T-ALL, suggesting involvement of alternate pathways compared with *KMT2A*r B-ALL and other T-ALL subtypes. *KMT2A*r T-ALL is a high-risk genomic subtype with no targeted therapies available, and further exploration of CD44 and *OPN* as potential therapeutic targets is warranted, to improve patient outcomes for this high-risk disease.

H011

Intensified therapy improves MRD responses in high risk AYA ALL. A report from the Australasian Leukaemia and Lymphoma Group (ALLG) ALL06 Study

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Aim: To evaluate MRD responses and survival in AYA ALL patients treated according to the high risk (HR) therapy arm of the ALLG ALL06 Study.

Method: ALL06 assessed deliverability of a paediatric protocol (ANZCHOG Study 8) in AYA ALL including the use of 1-6 HR blocks (median 2) in the 37 eligible patients, intended to reduce MRD prior to either allo-SCT or re-induction and maintenance. PCR-MRD responses and outcomes were evaluated for 35/37 pts who received ≥ 1 HR treatment (2 HR patients had no marker).

Results: Following HR treatment, 24/35 (69%) patients had improved MRD response or remained MRD negative. MRD responses were as follows: **MRD^{hi}** (N=11, 31%) - 2 became MRD^{neg}, 4 MRD^{lo}, 4 remained MRD^{hi}, 1 off study; **MRD^{lo}** (N=18, 51%) - 12 became MRD^{neg}, 5 remained MRD^{lo},1 became MRD^{hi}; **MRD^{neg}** (N=6; 17%) remained MRD^{neg} through HR therapy. 20/37 (54%) patients underwent CR1 allo-SCT, 3 year DFS and OS for patients proceeding to allo-SCT after HR treatment was 75% (95%CI, 56.0-94.0). N=10 medium-HR patients did not undergo a CR1 allo-SCT, 4 relapsed with 3 deaths. Finally, 7 came off study during HR therapy, 3 for relapse. For HR-treated patients who remain alive without relapse, there was a significant reduction in absolute MRD values in contrast to an increase in MRD in HR2 and HR3 (P=0.032 and P=0.038, respectively) in those that relapsed or died. 26/37 HR pts remain alive at last follow up with estimated 3-year DFS and OS of 63.4% and 69.3%, respectively.

Conclusion: HR therapy blocks were moderately effective at reducing MRD in high risk pts in ALL06. Outcomes compare favourably to HR cohorts from other study groups.

H012

Prognostic impact of monosomal karyotype in adult acute myeloid leukaemia – Western Australian experience.

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Aim: To describe the patient characteristics, treatment and survival outcomes of adult patients with monosomal karyotype acute myeloid leukaemia in Western Australia.

Method: Consecutive adults diagnosed with acute myeloid leukaemia (AML) with monosomal karyotype from 01 February 2016 to 01 April 2020 were identified from a laboratory database covering all public hospitals in Western Australia. Monosomal karyotype was defined as at least two autosomal monosomies or a single monosomy in the presence of at least one structural abnormality.

Results: Thirty-six patients were included in the study. The median age at diagnosis was 73 years (range, 19 – 85), and the majority of the patients were male (64%). AML was de novo (33.3%), therapy-related AML (36.1%) or secondary to myelodysplasia (27.8%). TP53 deletion was detected by FISH in 17 patients (47.2%). Intensive chemotherapy (idarubicin/cytarabine) was given for 6 patients and low-intensity treatment (azacitidine or low-dose cytarabine + thioguanine) for 10 patients. Only three patients (8%) achieved complete morphological remission and all had received intensive chemotherapy. More than half of the cohort received symptom care without chemotherapy (55.6%). Three patients (8.3%) were treated with allogeneic haemopoietic progenitor cell transplantation (HPCT) and the median time to transplant was 4.4 months (range, 3.6 – 5.2). Median survival was 3 months (95% C.I 1.84 – 4.06), and 1-year overall survival was 9.4% (95% C.I 4.3 – 14.5%). A single patient with >12-month follow-up remains alive; this patient underwent intensive chemotherapy followed by HPCT.

Conclusion: Monosomal karyotype in adults with acute myeloid leukaemia continues to portend a very poor prognosis in the modern era.

H013

Distinct differences between diagnosis and relapse of Ph-like acute lymphoblastic leukaemia in adolescents are revealed by single cell mRNAseq

Dr Susan Heatley[1,2,3], *Ms Jacqueline Rehn*[1,2], *Dr James Breen*[2,4,5], *A/Prof Andrew Moore*[3,6,7], *A/Prof Rosemary Sutton*[3,8], *Dr Michael Osborn*[3,9,10], *Prof Deborah White*[1,2,3,10,11]
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Aim: While the use of paediatric treatment protocols has improved outcomes for adolescents and young adults with acute lymphoblastic leukaemia (ALL), their survival remains inferior to younger children. This relates to adverse biological features, including poor drug tolerance and a higher incidence of Philadelphia (Ph)-like B-ALL. This subtype, which is associated with high relapse rates, exhibits considerable genomic heterogeneity and further understanding of this may reveal opportunities for targeted therapies. This study aimed to investigate the complex nature of the genomic alterations that occur in Ph-like ALL by single cell sequencing.

Method: Paired diagnosis and relapse samples from patients with Ph-like ALL were first flow-sorted on CD19 positivity. Single cells were isolated using the Fluidigm C1 system and the ClonTech SMART-Seq kit v4 was used for cDNA synthesis. The library was prepared using the Nextera XT DNA kit and sequenced on the Illumina NextSeq. Fusions were identified using FusionCatcher and variants using GATK HaplotypeCaller.

Results: Single cell mRNA sequencing was successfully achieved from three patients at both diagnosis and relapse with an average sequencing depth of 7 million reads and 1600 expressed genes per cell. Fusions and variants identified in the bulk population could be detected in each sample, however this varied between cells. Differential gene expression (top 100 genes) revealed there was a clear distinction in expression between cells at diagnosis and relapse. Interestingly, gene set enrichment analysis for each pair demonstrated down-regulation at relapse of MYC targets and up-regulation of TNF-alpha signalling.

Conclusion: This pilot study has demonstrated the feasibility of using single cell sequencing, with further experiments planned to interrogate a greater number of cells using the 10X Genomics platform. Moreover, this technology has provided insights into the genomic consequences of Ph-like ALL, with MYC and TNF-alpha identified as potential new targets for further exploration.

H014

In-vitro modelling of relapsed, refractory acute lymphoblastic leukaemia from a child with neurofibromatosis

Dr Susan Heatley[1,2,3], *Dr Elyse Page[1,4], Dr Laura Eadie[1,2], Dr Barbara McClure[1,2], Ms Jacqueline Rehn[1,2], Dr David Yeung[1,2,5,7], Dr Michael Osborn[2,3,6,7], Dr Tamas Revesz[2,3,6], Dr Maria Kirby[6], Prof Deborah White[1,2,3,4,7,8]*

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Case Study: Children with neurofibromatosis have a higher risk of developing juvenile myelomonocytic leukaemia and acute myeloid leukaemia, but rarely develop acute lymphoblastic leukaemia (ALL). A 9-year-old male with neurofibromatosis (germline *NF1* donor splice site mutation, c.1845G>A:p.L615=), was diagnosed with iAMP21 ALL and treated on AEIOP-BFM ALL2009 (high-risk due to minimal residual disease). Transcriptomic sequencing additionally revealed a *P2RY8-CRLF2* gene fusion and an *IKZF1* exon 2-3 deletion (Ph-like ALL). He relapsed three years later and proved refractory to salvage chemotherapy and blinatumomab. We further investigated mechanisms of resistance.

Whole exome sequencing identified an *NF1* c.7400dupT:p.L2467 frameshift (fs) mutation at relapse. The *P2RY8-CRLF2* gene fusion was transduced into the IL3 dependent B-ALL murine cell line Ba/F3 and the *NF1*fs was introduced by CRISPR/Cas9.

P2RY8-CRLF2 is not alone transformative, however a proliferation assay demonstrated, when co-expressed, the Ba/F3+*P2RY8-CRLF2*+*NF1*fs cell line was IL3 independent, indicating leukaemic transformation, whereas all other lines were not (Ba/F3, Ba/F3+*NF1*fs, Ba/F3+*P2RY8-CRLF2*). As NF1 is a negative regulator of RAS, increased activation of RAS and significant upregulation of pERK were confirmed by western blot in the *P2RY8-CRLF2*+*NF1*fs (vs Ba/F3, $p<0.0001$). In a 3-day cell death assay, only *P2RY8-CRLF2*+*NF1*fs demonstrated sensitivity to the MEK inhibitors trametinib and mirdametinib ($p<0.001$).

Germline *NF1* haploinsufficiency and a second hit *NF1* mutation in ALL is limited to one report of monozygotic twins with neurofibromatosis. Here, we have demonstrated a loss-of-function (LOF) *NF1*fs mutation using an *in-vitro* model of ALL. While the patient achieved remission with inotuzomab and underwent successful transplantation, we propose that *NF1* p.L2467fs caused bi-allelic LOF and therefore contributed to relapse. An understanding of the genomic complexities that lead to relapse may also inform personalised treatment strategies. The sensitivity to MEK inhibitors, currently in clinical trials for patients with plexiform neurofibromas or paediatric glioma, is an exciting development for neurofibromatosis patients with ALL

H015

Application of droplet PCR for detection of minimal residual disease in acute lymphoblastic leukaemia

Dr Michelle Henderson[1,2], *A/Prof Rosemary Sutton[1,2], Dan Chen[1,2], Libby Huang[1,2], Nicola Venn[1,2], Jodie Giles[1,2], Dr Toby Trahair[1,2], Tamara Law[1,2], Dr Vinod Vijay Subhash[1,2]*
[1]Children's Cancer Institute, Randwick, Australia, [2]UNSW Sydney, Randwick, Australia

Title: Application of droplet PCR for detection of minimal residual disease in acute lymphoblastic leukaemia

Background: Minimal residual disease (MRD) is routinely used to stratify patients and inform treatment decisions because it predicts higher risk of relapse. Real-time quantitative PCR (qPCR) measurement of patient-specific immunoglobulin/T-Cell Receptor (Ig/TCR) gene rearrangements, is commonly used. Droplet digital PCR (ddPCR) is a third-generation PCR technique with potential advantages, including absolute measurement, higher sensitivity, and higher tolerance of PCR inhibitors.

Aim: To investigate the benefits of ddPCR for MRD monitoring in paediatric ALL.

Method: We measured MRD by ddPCR on BioRad QX200 with 16 patient-specific IG/TCR assays (including frequently used consensus probes) and compared assay performance to qPCR.

Results: MRD levels in 210 follow-up samples from 15 paediatric ALL patients were measured by both qPCR and ddPCR. The quantitative range and sensitivity of both qPCR and ddPCR assay were the same for 9 patient-specific assays with superior performance of qPCR in 4 assays and superior results for ddPCR in 3 assays. Overall, the MRD levels detected by qPCR and ddPCR (85%) were in substantial agreement among 210 follow-up samples (Cohen's kappa coefficient, κ=0.76, P<0.0001), including 147 samples with PNQ or negative MRD levels, and 63 samples with quantifiable MRD levels. Among 63 samples with quantifiable MRD levels, the MRD levels between qPCR and ddPCR were highly correlated (Pearson's R^2=0.92, P<0.0001). Among 147 samples with non-quantifiable MRD level, there was a moderate agreement (79%) of MRD results between qPCR and ddPCR (Cohen's kappa coefficient, κ=0.52, P<0.0001).

Conclusions: Established qPCR assays are readily adapted to the ddPCR platform and quantified MRD levels are highly correlated. Contrary to common perception, ddPCR was not more sensitive than qPCR in this study. Given the cost of ddPCR, use of this technology for MRD monitoring may be limited to situations where other specific advantages apply.

H016

Clinical utility of Next Generation Sequencing in the diagnosis and management of myeloid malignancies

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Aim: Next Generation Sequencing (NGS) has an increasingly recognised role in the diagnostic workup, management and monitoring of patients with suspected myeloid malignancies, despite insufficient funding and limited availability. At our institution, a NATA accredited myeloid NGS targeted panel is offered to all patients with clonal myeloid disorders such as acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs). To highlight its value, we sought to describe the real-world use of a myeloid NGS panel at our institution and characterise its clinical utility.

Method: Peripheral blood or bone marrow from patients referred for diagnostic testing at Austin Pathology were analysed by a custom designed amplicon based 31-gene targeted NGS panel. Library preparation was done using Fluidigm Access Array System and variant calling was done using reporting software and standard curation procedure. The mean coverage of the assay was ~1000x with sensitivity of 3% for variant detection.

Results: 1102 samples were processed over a three-year period. Mutations were found in 88% of AML (n=189/216 cases), 86% of MDS (n=74/86 cases), and 98% of MDS/MPN overlap patients (n=39/40 cases) with morphologically confirmed diagnosis. 95% of MPN patients had mutations found (n=117/123 cases), majority of which were driver mutations (*JAK2*, *CALR*, *MPL*). A significant number of MPN patients showed additional coexisting mutations with driver mutations. Amongst cases of suspected MDS with indeterminate morphological features and cytopenias, 30% of cases had clonal mutations (n=36/122 cases). Amongst cases of suspected MPN due to persistent thrombocytosis, leucocytosis or polycythaemia, 13% had clonal mutations (n=52/400 cases). Our data has also uncovered novel variants and low allelic frequency variants that were missed by conventional assays and thus helped in supporting the diagnosis in few cases.

Conclusion: NGS testing has a powerful impact in myeloid malignancies in its ability of clarify diagnosis, shape prognosis and guide management choices including targeted therapies and transplantation. However, challenges remain in routine availability, funding and expertise needed for curation and variant interpretation.

H017

Detection of pathogenic germline variants following somatic panel-based next-generation sequencing

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Background: Inherited predisposition to myeloid malignancies is increasingly recognised and may be suspected based on relevant personal or family history of malignancy, antecedent cytopenias, and/or presence of mutations in implicated genes detected at high variant allele frequency (VAF) on somatic (tumour) sample testing [1, 2]. In Queensland, centralised somatic panel-based NGS testing for prognostication in myeloid disease has been available since October 2019. Here we describe the frequency and spectrum of suspected and confirmed germline mutations detected in the course of this testing.

Method: Sequencing data was reviewed from patients with AML, MDS and myelofibrosis who underwent NGS testing at initial diagnosis using the *Archer VariantPlex Core Myeloid* platform. Patients with mutations in candidate genes recognised by WHO as being of potential germline significance (*CEBPA, DDX41, RUNX1, ANKRD26, ETV6, GATA2 and TP53*) with VAF > 30% were analysed.

Results: Of 212 patients sequenced to date, 56 patients were included in this analysis. Confirmatory germline sample testing was performed in 14/56 (25%), using hair bulb in 85% and cultured skin fibroblasts in 15%. Germline testing rates were high (80-100%) for *DDX41* and *ANKRD26* mutations, but significantly lower for other suspected genes (Table 1). Germline mutations were confirmed in 7/14 patients with results pending at the time of submission in 3 patients.

Table 1.

Germline variants	Suspected with VAF>30%, n	Median age, years (range)	No. of patients tested, n	Confirmed germline, n	Results pending, n
CEBPA	10	57 (11-68)	0	0	0
DDX41	8	63 (58-71)	6	4	2
RUNX1	14	56 (4-68)	1	0	1
ANKRD26	1	49 (-)	1	1	0
ETV6	2	50 (48-52)	0	0	0
GATA2	3	45 (17-46)	3	1	0
TP53	14	62 (12-71)	3	1	0

Conclusion: Familial myeloid predisposition syndromes may be suspected following somatic NGS testing, however our data shows that the rate of confirmatory germline testing is low. This has implications for stem cell donor selection and cascade screening of relatives. For genes that are rarely somatically mutated in MDS/AML such as *DDX41* and *ANKRD26*, the likelihood of germline transmission is high and clinical vigilance is essential to ensure timely confirmatory sequencing. For other genes, germline testing may be more appropriately guided by the clinical scenario and our evolving understanding of the phenotype and management of these syndromes.

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H018

Epidemiology of adult acute promyelocytic leukaemia in New Zealand/Aotearoa

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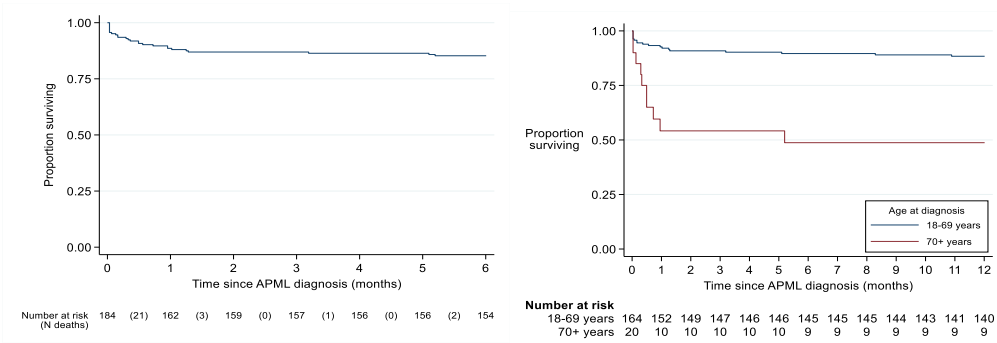
Aim: *Given the unique and important characteristics of acute promyelocytic leukaemia (APML), our aim was to describe the incidence over time, early mortality, and survival of patients with APML in New Zealand (NZ), using data from the New Zealand Cancer Registry (NZCR), cross referenced with national prescribing data (available from 2006).* [1]

Method: We extracted adult AML cases from the NZCR registry between 1 January 1997 and 31 December 2019. Cases with an ICD-10-CM code for AML and its subtypes including APML (C92.0) were included. Overall survival was calculated for APML cases, from the date of diagnosis to the date of death or last follow-up (31 December 2017). Kaplan-Meier analysis was used to estimate survival probabilities.

Results: During this 20-year period, 209 cases of APML and 3683 cases of AML (excluding APML) were reported to the NZCR (age ≥18 years). APML accounted for 5.4% of AML diagnoses in adults. At time of diagnosis, the average age was 49.2 years (11.0% were >70), with 52.1% males, and 63.5% European ethnicity, 16.4% Maori and 8.2% Pacific. The crude annual APML incidence was 0.28 per 100,000 on average (range 0.04-0.54). Average incidence rates increased slightly over the study period (r=0.40, p=0.05). Estimated 30-day and 1-year survival rates were 88.5% and 84.2% and differed significantly by age. For patients ≥70 the one month mortality rate was 50% versus 7.4% in the younger cohort. In the overall cohort the estimated 5-year survival rate was 82.2% for those surviving more than 30 days.

Conclusion: The incidence and rates of early death of APML in New Zealand is consistent with data from other western countries.[2,3] Early death was markedly higher in patients older than 70 and continues to represent an area of unmet need.

Figure 2: 6 month OS of the cohort (A) 12 month OS of the cohort stratified by age (B).



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H019

Unique transcriptome profile from platelets of patients with acute myeloid leukaemia: potential biomarkers of disease

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Background and Aim: Acute myeloid leukaemia (AML) is a heterogeneous disease driven by recurrent molecular mutations, epigenetic and cytogenetic aberrations. Tumour-educated platelets derived from solid organ malignancy are a promising source of biomarkers, however their applicability in haematological malignancy is not established. Here, we hypothesised that platelets from patients with AML have a unique gene expression profile distinct from healthy donors (HD).

Method: Platelets were isolated from AML patients (n=24) and HD (n=15) by differential centrifugation. Cytospins of the isolated platelets were assessed to exclude white blood cell contamination. Next generation sequencing of platelet transcriptomes, log2FC differential gene expression analysis was performed using DESeq2 where p-adj < 0.05 (using the Benjamini-Hochberg adjustment) was considered significant.

Results: Platelets from AML patients had a distinct gene expression profile compared to HD. Overall, 2691 genes were differentially expressed (padj<0.05, log2FC>±2), 2400 genes were overexpressed in AML (>4-fold) compared with HD while 291 genes were under-expressed. Significant overexpression of transcription factors, and proteases involved in cell replication and leukemogenesis were seen. The top 15 over-expressed genes include *MAFG, NFYC*, *HOXA7*, *PRTN3*, *MN1, PRSS57, ST18, ECRP, HOXB5, IL8, HOXA10, CBX2, LPPR3, MMP2,* and *WT1*. Expression of 6 of these genes were restored to normal (comparable to HD) when patients achieved remission. Upon disease relapse, increased expression was observed for all 6 genes. There was a significantly increase in expression of recurrently mutated genes associated with AML such as *FLT3, KIT, DNMT3A, TP53.* An increase in expression of *MN1*, *PRSS57*, *FLT3* or *DNMT3A* transcripts was detected at least 1 month (range 0.5-2) prior to haematological relapse.

Conclusion: Changes in platelet transcriptome occurs with AML disease states. Platelets may constitute a novel source of biomarkers for AML. Serial monitoring of these transcripts has a potential to inform early detection of relapse, prognosis and personalised interventional therapy.

H020

Quality-adjusted time without symptoms of disease and toxicity (Q-TWiST) analysis of CPX-351 versus 7+3 in older adults with newly diagnosed high-risk/secondary AML

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Aim: CPX-351 (Europe: Vyxeos® Liposomal; US: Vyxeos®), a dual-drug liposomal encapsulation of daunorubicin/cytarabine in a synergistic 1:5 molar ratio, is approved by the EMA and US FDA for adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes based on a pivotal phase 3 study (NCT01696084) in 309 patients aged 60 to 75 years with newly diagnosed high-risk/secondary AML. To evaluate both quality and quantity of life, we conducted a Q-TWiST analysis of the phase 3 final 5-year data in patients receiving CPX-351 versus 7+3.

Method: Overall survival for each patient was partitioned into 3 health states: TOX (time before response plus time with a grade 3/4 toxicity), TWiST (valuable time without relapse or grade 3/4 toxicity), and REL (time after relapse). Q-TWiST gain was assessed as the mean time spent in each state weighted by its respective quality of life, represented by health utility (U; scale of 0.0 [death] to 1.0 ["perfect" health]), calculated as (U_{TWiST}×TWiST)+(U_{TOX}×TOX)+(U_{REL}×REL). All analyses used a 1.0 TWiST utility weight. Relative Q-TWiST gains were calculated to compare clinical benefit across populations/studies.

Results: The relative Q-TWiST gains for CPX-351 versus 7+3 were considerably above the standard clinically important difference (CID) threshold of 15% for oncology for all patients (53.6%) and responders (39.8%). Across various sensitivity analyses, the relative Q-TWiST gains varied from 48.0% to 57.6% (**Table**).

Conclusion: This *post hoc* analysis suggests the survival benefit with CPX-351 for patients with high-risk/secondary AML is mostly from valuable time (TWiST), thus supporting the clinical benefit for patients. The relative Q-TWiST gains were well above the CID (15%) in the cancer literature and were maintained across various sensitivity analyses, supporting the robustness of the benefit. In the absence of direct quality of life measures, these results can be used together with the antileukaemia effect when considering treatment options.

Population	AEs	TOX utility weight	REL utility weight	Mean Q-TWiST gain (95% CI), days	Relative Q-TWiST gain[a]
ITT population[b]	All grade 3/4 AEs	0.5*TOX	0.5*REL	197 (76, 319)	53.6%
Responders[c]	All grade 3/4 AEs	0.5*TOX	0.5*REL	248 (−1, 496)	39.8%
Sensitivity analyses					
ITT population[b] *OR* Safety population[d]	All grade 3/4 AEs *OR* Treatment-related grade 3/4 AEs	0*TOX, 0.5*TOX, *OR* 1*TOX	0*REL, 0.5*REL, *OR* 1*REL	Ranged from: 177 (52, 302) to 212 (82, 342)	Ranged from: 48.0% to 57.6%

[a]Relative Q-TWiST gain was calculated as: Q-TWiST gain ÷ mean OS of control arm × 100.
[b]All patients who were randomised to induction treatment (CPX-351: n=153; 7+3: n=156).
[c]Patients achieving CR or CRi (CPX-351: n=73; 7+3: n=52).
[d]All patients who received ≥1 dose of study treatment (CPX-351: n=153; 7+3: n=151).

H023

Slide-based immunocytometry for diagnostics of acute leukemia

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Aim: Thailand reports about 2,800 new cases of leukemia per year, the two most frequent types being acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). While flow cytometry is the diagnostic gold-standard, a lack of qualified laboratories results in limited coverage and likely in underdiagnosis of leukemia, especially in provincial areas. Slide-based cytometry has the potential to improve accessibility: Automated immunostaining can easily be performed in provincial laboratories and slides can be scanned or shipped to larger medical centres, detaching expert diagnostic review from the site of sample processing. Our group previously reported cross-talk free, seven-colour fluorescence immunostaining on standard laboratory slides, coined “Cryoimmunostaining”. Here we examine the clinical utility of a six-colour leukemia diagnostic antibody panel.

Methods: An antibody panel targeting CD34, TdT, MPO, PAX5 and CD3 in combination with DRAQ5 nuclear staining was validated using Cryoimmunostaining in both cell line controls and blood samples of patients diagnosed with B-ALL, T-ALL and AML.

Results: Reproducible, clear staining results were obtained for membrane (CD34, CD3), cytosolic (MPO, cCD3) and nuclear antigens (TdT, PAX5). Nine cases of AML showed high MPO and a wide range of CD34 expression in large blast-like cells with pronounced anisocytosis and anisokaryosis. Five cases of B-ALL were bright positive for TdT with a wide range of PAX5 and inconsistent CD34 expression. Morphology was strikingly different from AML, with smaller isocytotic cell populations and more compact, isokaryotic nuclei. Two cases of T-ALL stained strongly positive for cCD3. Morphology was similar to B-ALL.

Conclusion: Results were condensed into an atlas of slide-based immunocytometry of acute leukemia, used as a reference system to analyse the results of an ongoing, larger, prospectively blinded diagnostic study. Further development of the atlas may also include training of a convolutional neural network to facilitate scale-up of remote cytoscreening.

H024

Knockout of HMGN1 in vivo reduces CRLF2r Down Syndrome Acute Lymphoblastic Leukaemia burden and increases survival outcomes

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Aim: Down Syndrome (DS) acute lymphoblastic leukaemia (ALL) patients experience higher treatment related toxicities and relapse rates compared to other ALL patients. Genes encoded on chromosome 21, including the high mobility group nucleosome-binding domain-containing protein 1 (*HMGN1*), may play a role in *CRLF2r* DS-ALL and is a potential therapeutic target. This study aimed to determine the leukaemic potential of *HMGN1* in *CRLF2r* DS-ALL using an *in vivo* CRISPR/Cas9 xenograft model.

Method: *CRLF2* was overexpressed in trisomy 21 SET-2 cells. NSG mice were engrafted with $3x10^5$ SET-2 *CRLF2* cells harbouring an inducible CRISPR/Cas9 *HMGN1* gRNA to initiate a knockout (KO) or control SET-2 *CRLF2* cells. Leukaemic progression was monitored using bioluminescent imaging (BLI) and *HMGN1* KO was induced with doxycycline following engraftment. Spleen, bone marrow and liver sections were stained with haematoxylin and eosin (H&E) at day 35 post engraftment and survival analyses were performed.

Results: Significantly, BLI of mice with induced *HMGN1* KO revealed a reduction in leukaemic burden over 24 days compared to the Cas9 control (Cas9:$3.6x10^6$±$2.3x10^5$, *HMGN1*:$6.5x10^4$±$1.9x10^4$, n=3-6;p<0.001). H&E staining demonstrated less leukaemic blasts present in organ sections harvested from *HMGN1* KO mice compared to Cas9 control mice, with reduced splenomegaly (Cas9: 81.7±7.86 mg, *HMGN1*: 51.67±3.7 mg;p=0.046). Blood counts at day 35 indicated thrombocytopaenia and anaemia in Cas9 mice (platelet: 705±43 K/µL, HCT: 22.5±2%) that was not observed in *HMGN1* KO mice (platelet: 1503±83 K/µL;p<0.001; HCT: 38±3.4%;p=0.004).Of importance, survival analysis of the remaining *HMGN1* KO mice indicated a survival advantage, from 35 days (Cas9) to 56 days, for *HMGN1* KO mice (p=0.0009).

Conclusion: Knockout of *HMGN1* mitigated ALL phenotypes including hepatosplenomegaly, anaemia and thrombocytopaenia, preventing leukaemia progression and resulting in a significant survival advantage over Cas9 mice. This suggests, *HMGN1* is causatively linked to DS-ALL and is a potential candidate for the development of a pharmacological inhibitor for *CRLF2r* DS-ALL

H025

Lineage skewing of IDH mutant pre-leukemic stem cells

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Background: *Presence of blood cells with mutation of DNMT3A, TET2 or ASXL1 are frequently identified in patients with acute myeloid leukaemia (AML) in morphologic remission. These cells have been called pre-leukemic stem cells because (1) they do not harbour other mutations present in the diagnostic AML sample (e.g. NPM1) (2) they have retained differentiation potential and (3) they may persist for years without giving rise to relapse. Pre-leukemic stem cells may also harbour IDH mutations although little is known about the cell of origin.*

Aim: To assess the differentiation capacity of the cell that harbours IDH1/2 mutations in AML patients in morphological remission.

Method: Five patients with IDH1 or IDH2 mutated AML with persistent IDH1/2 mutations in morphological remission were retrospectively identified. Peripheral blood cells expressing CD34, CD19, CD3 and CD33 were isolated using magnetic beads and the level (VAF %) of IDH mutation in each of these cell fractions measured using quantitative digital droplet PCR methodology. This study was approved by Ethics (project no. 39/12).

Results: Five patients with AML in morphological remission and persistent IDH1/2 mutations were identified and summarised in Table 1. Three patients had concomitant NPM1 mutations, all three of whom were NPM1 MRD negative in morphological remission. The IDH1/2 VAF % range from <1% to close to 50%.

Table 1- VAF % in various cell compartments

Patient	Age/sex	Mutation	Baseline CG	Time from initial diagnosis (mo)	Duration of current remission (mo)	Concomitant mutations	CD3 IDH VAF %	CD33 IDH VAF %	CD34 IDH VAF %	CD19 IDH VAF %
1	79F	IDH1 R132C	NK	210	20	NPM1 DNMT3A	1.77	47.4	43.5	45
2	66M	IDH1 R132C	NK	226	169	Nil	1.39	16.3	13.5	17
3	69M	IDH1 R132H	t(6;14), der(6)+	57	57	NPM1 FLT3-ITD	0.08	0.566	1.14	2.87
4	63F	IDH1 R132S	NK	109	73	NPM1 DNMT3A	1.45	47.5	36.2	33.8
5	72F	IDH2 R172K	Trisomy 8	51	17	Nil	5.34	29.6	39.6	26.4

CG- cytogenetics, NK- normal karyotype

Conclusion: We demonstrate that patients with persistent IDH1/2 mutations in remission have the mutations at the stem cell level (CD34) but with low T cell (CD3) compartment distribution. This may imply impaired T-cell differentiation in IDH-mutated progenitor cells. Further analysis of cellular distribution of IDH mutations along with other baseline mutations in diagnostic samples is underway.

H026

Efficacy and safety of Venetoclax in treatment of relapsed refractory Acute Myeloid Leukaemia: a single centre real world experience

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Aim: to document safety and efficacy of venetoclax when used in the treatment of relapsed refractory (RR) acute myeloid leukaemia (AML) at our institution.

Method: retrospective audit of electronic medical records for 20 consecutive patients receiving venetoclax at University Hospital Geelong between November 2018 and May 2021.

Results: 20 patients received venetoclax for treatment of CLL (n=6, excluded) or RR AML (n=14). 14 AML patients (50% male) with median age 67 years (43-82 years) were ECOG 1 (29%), 2 (43%) or 3 (29%) at commencement of treatment. Fifty-seven percent of patients had secondary AML, 86% were high risk and 14% were intermediate risk by 2017 ELN classification[1].
Patients had median one prior line of therapy (range 1-4), including intensive chemotherapy in 36% and allogeneic stem cell transplant in 29%. Venetoclax was initiated at 100mg daily with posaconazole 300mg daily for 28 day cycles, as monotherapy (7%) or in combination with azacitidine (72%) or low dose cytarabine (21%). Venetoclax median treatment duration was 28 days (range, 11 - 222) and 50% patients achieved CR/CRi with a median time to CR/CRi of 24 days (range, 21-108). After median follow up time of 163 days (range,15 - 840), 57.1% patients died and median overall survival was 5.8 months (range 0.5-30).
Venetoclax therapy was eventually discontinued in 78.5% patients, due to patient proceeding to alloSCT (18.2%); ≥Grade 3 infective toxicity (27.3%) or treatment failure (54.5%). Observed toxicities of ≥Grade 3 severity included neutropenia (35.7%), febrile neutropenia (78.6%), anemia (64.3%) and thrombocytopenia (28.6%). Infections leading to cessation of venetoclax due to toxicity were E. Coli bacteremia (n=1), appendicitis (n=1) and MRSE osteomyelitis (n=1).
Conclusion: Our CR/CRi, OS and treatment discontinuation rates compare favourably with the recently published Spanish multicentre experience (CR/CRi 11%, median OS 2.8 mths, toxic discontinuation 28%)[2] and with the 24% reported discontinuation of venetoclax and azacitidine in the upfront setting[3].

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H027

An Australian experience of immune effector cell associated neurotoxicity syndrome (ICANS) in patients treated with standard of care tisagenlecleucel for B cell acute lymphoblastic leukaemia (B-ALL)

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Aim: Here we report the incidence and characteristics of ICANS, a potentially devastating complication of chimeric antigen receptor T-cell (CAR-T) therapy[1,2,3], in the largest cohort of Australian patients with B-ALL treated with tisagenlecleucel.

Method: Patients at Peter MacCallum Cancer Centre and the Royal Children's Hospital who received commercial tisagenlecleucel for B-ALL from 2019 to April 2021 were identified from our database (HREC 2016.305, 68560) and records were reviewed retrospectively.

Results: 29 patients were identified. Five (17%) had ICANS, with their details summarised:

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, sex	23, female	20, male	11, male	14, male	12, female
Lines of prior treatment	7	5	5	1	6
Prior AlloSCT	Yes	Yes	Yes	No	Yes
Prior radiotherapy	Yes	Yes	No	No	Yes
CNS involvement	Yes	Yes	Yes	Yes	Yes
CRS grade	2	2	3	NA	2
Tocilizumab exposure	Yes	Yes	Yes	No	No
Neurological symptoms	Confusion, altered behaviour, dysphasia	Anisocoria, photophobia	Confusion, agitation, photophobia	Slowed mentation, aphasia, global motor deficit	Somnolence, aphasia, global motor deficit
Day of onset (post infusion)	7	9	7	37	7
ICANS grade	3	1	3	4	4
MRI findings	Bifrontal leptomeningeal enhancement, white matter T2/FLAIR hyperintensity, microhaemorrhages	White matter T2/FLAIR hyperintensity	Nil acute changes	White matter T2/FLAIR hyperintensities	White matter T2/FLAIR hyperintensities
CSF findings	-	-	Mature lymphocytes in CSF	No significant lymphocyte population	No significant lymphocyte population
EEG findings	Diffuse slowing	-	-	Diffuse slowing	Diffuse slowing
Treatment	Intravenous dexamethasone	Intravenous dexamethasone	Intravenous dexamethasone	Intravenous dexamethasone, intravenous immunoglobulin, levodopa	Intravenous methylprednisolone, dexamethasone, dasatinib
Outcome	Resolved over 36 hours	Resolved over 4 days	Resolved over 4 days	No improvement	No improvement

Conclusion: In this early Australian experience, the incidence of ICANS in B-ALL patients was lower than reported in a previous international cohort (27.1%)[4]. Notably, the clinical and radiological features seen in our cases were diverse, with variable response to treatment. Prospective neurological assessments may help to clarify specific ICANS risk factors.

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H028

Combined whole genome and transcriptome sequencing improves subtype classification in AYA/adults with B-acute lymphoblastic leukaemia

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Aim: Genomic analysis has driven subtype discovery and risk stratification in B-acute lymphoblastic leukaemia (B-ALL). Whole genome sequencing (WGS) and whole transcriptome sequencing (WTS) is required for classification of genomically complex and clinically relevant subtypes that may not be detected by conventional cytogenetics/FISH. We aimed to determine the utility of WGS/WTS for subtype classification compared to cytogenetic analysis.

Method: Genomic profiles from 37 AYA/adult patients including 29 newly diagnosed and eight relapsed B-ALL were defined using subtypes described previously[1]. Combined WGS/WTS assessment incorporated somatic coding and non-coding mutations, structural variants and copy number abnormalities using the UMCCR Genomics Platform, and gene expression using the ALLSorts B-ALL classifier. WGS/WTS was compared to standard of care cytogenetics and FISH.

Results: 19 of 37 patients were classified by cytogenetics/FISH with all classifications concordant with WGS/WTS findings. Of 18 patients unclassified by cytogenetics/FISH ("B-other"), WGS/WTS identified genomic findings in 15 patients (83%) allowing further genomic classification. These included Ph-like (n=5), DUX4 (n=3), PAX5alt (n=3), Low hypodiploid (n=2), MEF2D (n=1), ZEB2/CEBP (n=1). Comparing WGS (DNA-based) and WTS (RNA-based) analysis for 32 patients with comparative data, 18 patients would be correctly classified by either approach, three by WGS-only, three by WTS-only, and eight required the combination of WGS/WTS to make a correct classification. Three patients who remained "B-other" following WGS/WTS were enriched for novel IGH translocations. Furthermore, three cases had genomic evidence supporting classification as two subtypes.

Conclusion: In our cohort, WGS/WTS provided accurate genomic subtype classification in a greater proportion of patients (92%) compared to standard of care cytogenetics/FISH (51%). Importantly, the combination of WGS and WTS was also superior to WGS-only or WTS-only for correct genomic subtype assignment. The feasibility, utility to improve clinical outcomes and health economic impact of WGS/WTS warrants assessment in larger cohorts.

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H029

Novel genomic alterations of NOTCH1 detected by whole genome sequencing in T-acute lymphoblastic leukaemia/lymphoma and implications for clinical risk stratification

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Aim: NOTCH signalling is critical for T-cell lineage commitment as evidenced by the high frequency (>50%) of activating *NOTCH1* mutations in T-acute lymphoblastic leukaemia/lymphoma (T-ALL). Clinically, *NOTCH1* mutation status has been incorporated into molecular risk scores for prognostic stratification. Given sequencing studies have focused on heterodimerisation and PEST domain mutations, we aimed to investigate non-canonical alterations by performing whole genome sequencing (WGS) in a cohort of *NOTCH1*^{mut} and *NOTCH1*^{wt} T-ALL.

Method: We identified 50 patients with T-ALL referred for diagnostic targeted sequencing (Lymphoid/PanHaem Panels) to the Molecular Haematology Laboratory at the Peter MacCallum Cancer Centre, Melbourne, Australia. WGS was performed on 14 cases including four *NOTCH1*^{wt}, and somatic analysis for coding and non-coding mutations, structural variants and copy number abnormalities performed using the UMCCR Genomics Platform.

Results: Targeted sequencing of *NOTCH1* exons 25-28 and 34 corresponding to the heterodimerisation/PEST domains identified 41 mutations in 32 patients (64%). In order to investigate the presence of *NOTCH1* alterations missed through targeted sequencing, WGS was performed on four *NOTCH1*^{wt} cases. Non-canonical somatic *NOTCH1* alterations were identified in three of four cases including (i) a novel p.(Ala19Pro) mutation occurring in the extracellular domain, (ii) a t(2;9)(q34;q34) involving *IKZF2-NOTCH1*, and (iii) intragenic *NOTCH1* deletion of exons 3-27 predicted to result in an N-terminal truncated protein. WGS also identified a focal duplication of the *NOTCH1* enhancer of MYC (N-Me) in a *NOTCH1*^{mut} case.

Conclusion: Through comprehensive genomic analysis we have expanded the spectrum of somatic *NOTCH1* alterations in T-ALL to include structural variants, exon deletions and enhancer duplication. Our data suggests that the frequency of genomic alterations leading to *NOTCH1* activation may be higher than previously reported and that targeted sequencing is insufficient to detect all abnormalities. This has significant clinical implications for the implementation of *NOTCH1*-based risk stratification which does not consider these non-canonical alterations.

H030

Hyperleukocytosis associated with delayed presentation among patients with acute leukaemia during the COVID-19 pandemic in Victoria

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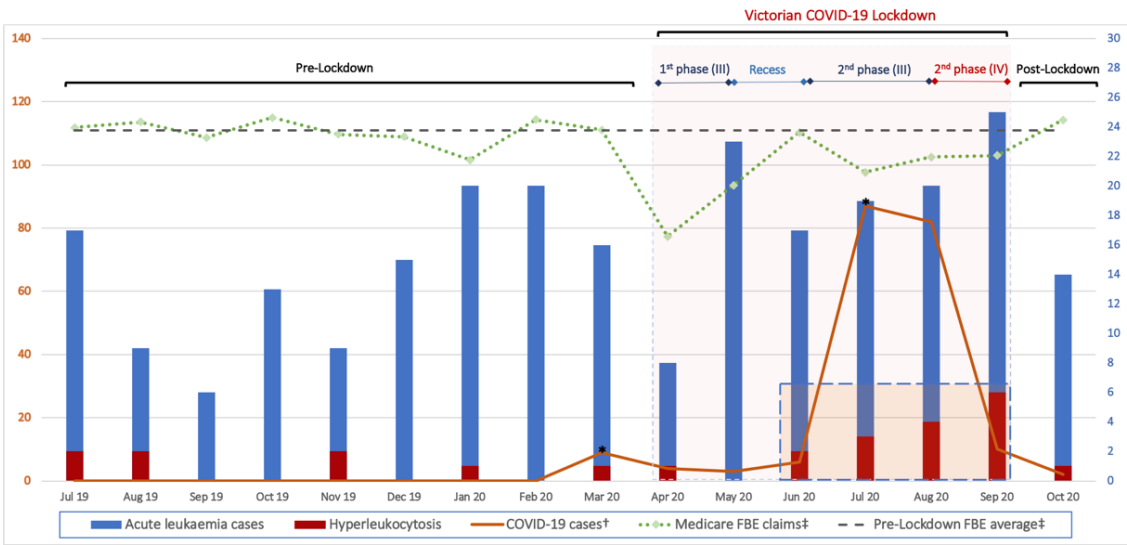
Aim: Civil restrictions during the COVID-19 pandemic resulted in a temporary decline in new cancer diagnoses in Victoria.[1] We hypothesised that delayed presentation would result in a higher frequency of hyperleukocytosis (HL; WCC > 100 x10^9/mL) in patients w/ acute leukaemia (AL).

Method: Newly-diagnosed (ND) AL from 6 centres (Alfred-Monash-RMH-Austin-SVHM-Northern) were retrospectively collected between Jul-19 to Sep-20. There were two COVID-19 case peaks (Mar & Jul-20), a 6-month 'lockdown' (Apr to Sep-20) & a preceding 9-month 'pre-lockdown' period (Jul-19-Mar-20) (**Fig. 1**). Monthly aggregate FBE claims (surrogate for test numbers) in Victoria were accessed from Medicare Online (www.servicesaustralia.gov.au; 13-04-21).

Results: 237 cases were recorded during the entire study period (174 AML, 33 ALL, 30 APML). With respect to ND-AL cases during the 1st restriction, there was a ~50% reduction in Apr-20 (n=8), compared to the median monthly number (n=15) pre-lockdown, with a rebound in May-20 (n=23) (**Fig. 1**). A 33% rise in median monthly case numbers was observed during the 2nd restriction, which peaked in Sep-20 (n=25). A 30% reduction in Medicare FBE claims were also noted during Apr-20 (corresponding with reduced incident AL cases), followed by a second, more sustained reduction from Jul- to Sep-20. Associated with this was a period of increasing HL frequency for 4 consecutive months (Jun- to Sep-20) during the 2nd restriction. Overall, HL frequency was significantly higher during lockdown (14% vs 6% pre-lockdown, p=0.045); with higher baseline WCC also observed (median 10.7 vs. 5.4 x10^9/mL, p=0.043). New AL case numbers, HL frequency & FBE claim activity returned to baseline by Oct-20 (**Fig. 1**).

Conclusion: The potential delay in AL diagnosis related to reduced FBE testing activity during COVID-19 enforced civil restrictions resulted in reduced AL case numbers (Apr-20) followed by a rebound phase with increased frequency of HL. Our study confirms that a short-term delay in diagnosis, in the context of pandemic-associated restrictions, can result in a measurable impact on the natural history of highly proliferative cancers & increased HL presentations in patients with ND-AL.

Fig. 1. FBE activity, COVID-19, AL cases & hyperleukocytosis during the COVID-19 pandemic



H031

Validation of an acute myeloid leukaemia measurable residual disease flow cytometric analysis method using Kaluza software and multidimensional radar plots

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Aim: The aim of this study was to create a template using the multidimensional radar plot function in Kaluza software to detect measurable residual disease (MRD) in acute myeloid leukaemia and to compare it to the current analysis method.

Method: We used Kaluza software to create a template utilizing multidimensional radar plots to analyse AML MRD samples. To validate this method, we compare the results of our method with the current method for 80 consecutive adult samples received for MRD. Statistical analysis was completed using the Cohen's Kappa and McNemar analysis methods.

Results: The two MRD analysis methods showed a moderate correlation (k = 53%) with no difference between the two methods (p = 0.16). Analysis of the low-level MRD results between 0.01 to 0.1% showed a significant difference between the two groups. (n=22, p=0.004). Ten of the participants in this group were positive by the radar plot method, but negative by the current method. Molecular results were available for 25/80 cases. The agreement between the radar plot method and molecular analysis was fair with no significant difference between the two methods. (k=30%; p=0.18).

Conclusion: There is a moderate agreement between the two MFC methods, suggesting the radar plot method is fit for purpose. The increased number of samples positive for low-level MRD suggest the radar plot method may be more sensitive. Confirmation of this finding is necessary. The discrepancies with the molecular method may be due to the increased sensitivity of molecular tests, expansion of leukaemic subpopulations or non-leukaemic myeloid populations that may confound MRD result interpretation. The next steps are to implement this analysis method into the diagnostic laboratory.

H032

Hypoglycaemia secondary to PEG-asparaginase in acute lymphoblastic leukaemia

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Background: Hypoglycaemia secondary to L-asparaginase therapy for acute lymphocytic leukaemia (ALL) has been described in the literature[1-3] but to date only cases of hyperglycaemia have been associated with PEG-asparaginase[3]. Here we describe the first reported case of fasting hypoglycaemia associated with PEG-asparaginase use in ALL.

Case: A 19-year-old male was diagnosed with t-ALL after presenting with a large mediastinal mass. He was commenced on FRALLE 2000 induction therapy including Prednisolone, PEG-asparaginase, Vincristine, Daunorubicin, Cyclophosphamide and triple intrathecal therapy. He had nil other relevant medical history with the exception of a high BMI >40, for which his PEG-asparaginase dose was reduced. His blood sugar levels (BSL) were monitored daily whilst on Prednisolone given his body habitus. Prior to administration of PEG-asparaginase on Day 8, BSLs were found to be in normal limits. After receiving his first dose of PEG-asparaginase (500IU/m2) he was noted to have lower fasting BSL but still within acceptable ranges. It was three days after his Day 22 dose of 1000IU/m2 he began to experience repeated fasting hypoglycaemic levels of between 2.4-4mmol/L. He was symptomatic at times, with one event requiring readmission to hospital for symptom management. It was noted his hypoglycaemia timing correlated with low antithrombin levels from his PEG-asparaginase therapy. There was also resolution of his hypoglycaemia that coincided with restoration of normal antithrombin levels, leading us to suspect his hypoglycaemic events were secondary to his PEG-asparaginase. Endocrinology was consulted who found nil other aetiology for his fasting hypoglycaemia.

Conclusion: We report the first case of fasting hypoglycaemia secondary to PEG-asparaginase therapy in t-ALL, an essential component of ALL therapy. While monitoring is often done for the known side effects of coagulopathy, acute pancreatitis, hepatotoxicity and hyperammonaemia it is important to monitor BSLs for hypo- as well as hyperglycaemic events.

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H033

Acute Myeloid Leukemia and Pulmonary Alveolar Proteinosis- successful therapy with concomitant venetoclax / low dose cytarabine and nebulised GMCSF.

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Aim: Pulmonary Alveolar Proteinosis (PAP) is a rare lung condition with lipoproteinaceous alveolar accumulation [1,2]. PAP can be primary or secondary to disorders including haematological malignancies, namely myelodysplastic syndrome (MDS)[1]. Inhaled sargramostim a recombinant granulocyte–macrophage colony-stimulating factor (GMCSF) is safe and effective therapy for PAP [3]. We report a PAP patient preceding a MDS diagnosis, subsequently transforming to acute myeloid leukaemia (AML), treated successfully with nebulised sargramostim and concomitant venetoclax and low dose cytarabine (LDAC).

Method: Eastern Health ethics informed consent was obtained.

Results: A 77 year old woman with PAP underwent initial therapeutic bilateral bronchoalveolar lavage (BAL) with symptom resolution for two years. Between BALs, she was diagnosed with MDS-EB2 with 11% bone marrow (BM) blasts; normal cytogenetics and no targetable mutations. Azacitidine was commenced with clinical benefit for 16 months, before progression to AML with 20% BM blasts. 'Induction' with combined LDAC (10 days) and compassionate access venetoclax (14 days) achieved BM hypocellularity with 1% blasts after 1 month. She remains in clinical remission currently up to her fifth maintenance cycle of dose-reduced LDAC (10 days) with venetoclax (10 days). Concurrent with AML transformation, her PAP respiratory symptoms worsened requiring hospitalisation for oxygen therapy but the patient declined further BAL. Based on Tazawa et al [3], a 12 cycle, six months nebulised GMCSF protocol was commenced. After two GMCSF cycles, 40% high flow oxygen requirement reduced to her domiciliary baseline of 2 L/min via nasal prongs. Correlative CT chest showed moderate reduction in "crazy paving" appearance. Currently on her fifth month of GMCSF, baseline comparative lung function tests will be reassessed upon completion of full GMCSF therapy

Conclusion: Herewith, a case of synchronous PAP with MDS-AML successfully treated non-invasively with inhaled GMCSF and LDAC and venetoclax with resultant remission and maintenance of good quality of life.

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H034

A Comprehensive Analyses of Ph+ ALL Paediatric/AYA and Adult Patients using Next Generation Sequencing and Flow Cytometry.

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Aim: Deep sequencing has recently revealed the genomic basis for many cases of non-Ph+ ALL, though this data is lacking for the Ph+ group. Here we use a variety of approaches to fully characterise Ph+ ALL, a high-risk subset.

Methods: Transcriptomic sequencing (mRNAseq) was performed on 120 patient samples (age 2-76) of which 102 were diagnostic/18 relapse. Flow cytometry determined blast cell phenotype, phospho-flow cytometry assessed drug sensitivity and multiplex ligation-dependent probe amplification informed candidate gene copy number.

Results: mRNAseq revealed the *BCR-ABL1* e1a2 fusion (p190) in 73% of cases (Fig 1A). Karyotype analyses revealed t(9;22) was present in all patients, while 70% also demonstrated other abnormalities, including aneuploidy. *IKZF1* deletions were detected in 68%, most monoallelic. 79% had loss of one or both allele of key B lymphoid development/transcriptional regulation genes. Most commonly *CDKN2A/B* (55%/43%), *PAX5* (48%), *BTG1* (27%) and *RB1* (17%). 84% of these coincided with *IKZF1* deletions. Most samples were responsive by phospho-flow to Abl TKIs but not ruxolitinib.

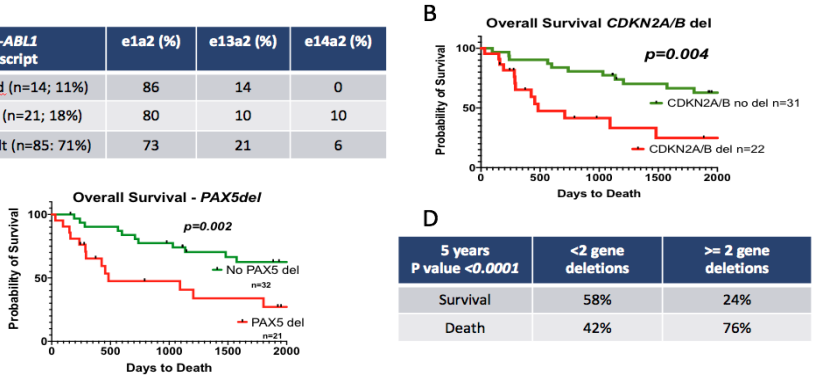
mRNAseq detected few structural variants common in other B-ALL subtypes. Importantly, *ABL1* mutations were only detected at relapse. *ABL2* variants were detected in 8 patients at diagnosis, *CBL* in 4 and *CSF1R* in 15. Altered genes (ie:*RUNX1, ASXL1, TP53*) previously detected in high-risk CML patients were not detected.

Survival analyses of 53 patients revealed deletions in *IKZF1* did not predict 5 year overall survival (OS)(*p=0.132*), but deletion of *PAX5* and *CDKN2A/B* (Fig 1B,C) did. Inferior OS was also observed with multiple gene deletions (Fig 1D).

Conclusion: The genomics of Ph+ ALL is distinct from other B-ALL's and CML at the genomic level. While *BCR-ABL1* remains central to pathogenesis, mutations in other genes beside B-cell transcription, cell cycle and tumour suppressor pathways are scarce. Work is ongoing to further refine risk stratification in this patient group.

A

BCR-ABL1 transcript	e1a2 (%)	e13a2 (%)	e14a2 (%)
Paed (n=14; 11%)	86	14	0
AYA (n=21; 18%)	80	10	10
Adult (n=85: 71%)	73	21	6



D

5 years P value <0.0001	<2 gene deletions	>= 2 gene deletions
Survival	58%	24%
Death	42%	76%

Figure 1: A. Transcript type across the age groups. **B &C** Survival based on the presence or absence of a *CDKN2A/B* and *PAX5* deletion. **D.** Survival based on the number of gene deletions present.

H035

Peripheral Blood Stem Cell Mobilization with First-in-Class or Biosimilar Granulocyte Colony-Stimulating Factor: A Retrospective Study

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Aim: Autologous stem cell transplant is an integral hematologic malignancy therapy. Granulocyte Colony-Stimulating Factor (G-CSF) is vital to the mobilization of hematopoietic stem and progenitor cells, promoting ready leukocytopheresis collection of CD34+ autologous cells for transplant. Multiple G-CSF biosimilars exist at varying pricepoints. We sought to determine whether mobilization efficacy varied between filgrastim (Neupogen) and the G-CSF biosimilar zarxio (Zarzio).

Method: We performed a retrospective chart review on patients undergoing autologous stem cell leukapheresis between January 2019- December 2020. We collected demographic and clinical patient data, including mobilization strategy and pre-collection peripheral CD34 count (CD34). We compared CD34 counts of patients mobilized with filgrastim versus zarxio with a Mann Whitney U test. $P<0.05$ was statistically significant.

Results: 37 patients were mobilized with filgrastim (N=11) or zarxio (N=26). Patient demographics were similar (Table). There was no statistically significant difference in the pre-collection CD34 counts between the two groups of mobilized patients (Table).

Conclusion: This small case series identified no statistically significant difference in CD34 mobilization between filgrastim and the G-CSF biosimilar zarxio, suggesting that the lower cost G-CSF (zarxio) may not result in poorer mobilization as compared to filgrastim. Larger comparative studies would strengthen these conclusions.

Table: Patient Demographics and CD34 Mobilization Efficacy

Patents	Zarxio	Neupogen	
Total, n (%)	26 (70%)	11 (30%)	
Gender, n (M, F)	22, 4	7, 4	
Age, years (IQR)			
Diagnosis, n			
Multiple Myeloma	8	5	
Amyloidosis	6	3	
Lymphoma/Leukemia	9	3	
Waldenstrom/Other	3	0	
Mobilization Efficacy			P value
Pre-collection CD34+ cells/ul, median (IQR)	17.3 (5.5-31.9)	16.5 (6.0-28.5)	0.94

H036

Variable impacts of venetoclax and ruxolitinib on recipient immunity improve alloSCT outcomes in mice.

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Aim: Allogeneic stem cell transplantation (alloSCT) cures haematological malignancies, but is associated with graft versus host disease (GVHD), infection, and transplant-related mortality. Mitigated pre-transplant conditioning in combination with short-term pharmacological inhibition of recipient immune cell function may promote donor cell engraftment and limit GVHD. We explored the role of IL-15, JAK1/2 and BCL2 in recipient natural killer (NK) and T cells in regulating donor cell engraftment and GVHD in murine alloSCT recipients.

Method: Mouse models of MHC-mismatched alloSCT: C57BL/6 wild-type or IL-15 knockout mice were given myeloablative irradiation (2 x 600 rad), or reduced intensity conditioning (RIC; 2 x 400 rad), and an i.v. injection of 7.5e6 BALB/c BM + 1e6 T cells. Alternatively, WT recipients were treated with ruxolitinib for two days by oral gavage twice daily (180 mg/ml), followed by RIC and alloSCT. Preclinical model of AML: WT mice were injected i.v. with MLL-AF9 tumour cells, and administered 180 mg/ml ruxolitinib twice daily by oral gavage on days 8 and 9. On day 10 mice received RIC and alloSCT. Mice were monitored for donor cell engraftment, GVHD and GVL responses. Flow cytometry and Nanostring gene expression analysis was performed on BM collected from mice treated for two days with either venetoclax (100 mg/ml), ruxolitinib (180 mg/ml) or vehicle.

Results: IL-15 deficient alloSCT recipients developed hyperacute GVHD, whereas ruxolitinib treatment in combination with RIC promoted rapid donor cell engraftment and GVL responses, but skin GVHD developed in 25% of mice. Investigation of short-term BCL2 or JAK1/2 inhibition on the recipient immune system revealed a striking difference in their mechanisms of action on immune cell subsets, and furthermore in regulating MHC class-II and interferon-inducible gene expression.

Conclusion: Repurposing clinically-approved drugs to briefly inhibit recipient immune cell function, in combination with RIC, may represent a means by which to deliver alloSCT more safely.

H037

Characteristics and treatment burden of chronic graft-versus-host-disease in the modern era.

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Aim: To characterise chronic graft-versus-host-disease (cGVHD) outcomes in a single institution for adults undergoing allogeneic progenitor cell transplantation.

Method: All adult patients who received matched unrelated or HLA-identical sibling donor allogeneic peripheral blood progenitor cell transplantation at Fiona Stanley Hospital (WA) from 1 February 2015 to 31 December 2019 were included. Chronic GVHD data was retrieved from an assessment form based on the NIH consensus guidelines which was prospectively completed by physicians at every outpatient clinic appointment. The probability of cGVHD was calculated using cumulative incidence analysis to accommodate competing risks.

Results: One hundred and forty-nine patients were included. Most patients had matched unrelated donors (65.1%) and were treated with standard ciclosporin and methotrexate GVHD prophylaxis (98.7%) without ATG (85%). The median follow-up was 30.6 months (range, 12.1 – 59.1 months). The cumulative incidence of any cGVHD at 1-year was 67.6% (95% C.I 58.2 – 75.6%); moderate or severe was 28.3% (95% C.I 20.5 – 36.7%); and severe was 8.3% (95% C.I 4.2 – 14.1%). The organs most commonly involved by cGVHD of any severity were mouth, liver and skin. The most commonly involved organ in severe cGVHD was the liver (77%), whereas for moderate cGVHD it was the mouth (77%) (**Figure 1**). The 12-month cumulative incidence of transplant-related mortality was 17.5% (95% C.I. 11.8 – 24.0%). At 12 months after transplant, 71% of survivors remained on immunosuppression, and 50% remained on immunosuppression at 24 months.

Conclusion: Prospective, meticulous documentation of cGVHD according to NIH guidelines revealed a high burden of cGVHD in this cohort of mostly unrelated donor recipients who received standard prophylaxis without ATG.

H038

Outcomes from the first five years of allogeneic haemopoietic progenitor cell transplantation at Fiona Stanley Hospital.

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Aim: To describe the patient demographics, transplant and survival outcomes of allogeneic haemopoietic progenitor cell transplantation (alloHPCT) at Fiona Stanley Hospital (WA) since its establishment in 2015.

Method: One hundred and ninety-three consecutive adult patients who had alloHPCT were identified retrospectively from 1 February 2015 to 31 December 2019. Pre-transplant, transplant and clinical outcome characteristics were analysed.

Results: Acute myeloid leukaemia (AML) was the most common indication for transplant (n = 82, 42.5%) followed by myelodysplasia (16.1%). The median time from diagnosis to alloHPCT in patients with AML in first complete remission was 5.7 months (range, 2.4 – 28.4). The cumulative incidence of grade III-IV aGVHD at 6 months was 10.4% (95% CI 6.5 – 15.4%) and the cumulative incidence of severe cGVHD at 2 years was 10.2% (95% CI 5.7 – 16.3%). The median follow-up was 24.3 months (range, 5.9 – 62.1). Overall survival at 1 and 2 years was 73.7% (95% CI 70.1 – 77.3%) and 65.0% (95% CI 61.2 – 68.8%) respectively. Progression-free survival at 2-years was 62.9% (95% CI 59.6 – 66.2%). The cumulative risk of transplant-related mortality at 2-years was 17.8% (95% CI 12.6 – 23.7%), and disease relapse at 2-years was 19.3% (95% CI 13.8 – 25.6%).

Conclusion: Clinical outcomes of allogeneic transplantation at Fiona Stanley Hospital appear acceptable and are comparable to those reported elsewhere within Australia and overseas. This information is valuable for transplant physicians, referrers and patients in Western Australia and will inform future practice improvement activities.

H040

Outcomes of defibrotide-treated patients with anicteric/icteric veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) after haematopoietic cell transplantation (HCT): results from the EBMT registry

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Aim: VOD/SOS is a potentially life-threatening complication of HCT. Hyperbilirubinaemia is a key criterion for VOD/SOS diagnosis, although recent guidelines also acknowledge VOD/SOS without elevated bilirubin. In an expanded-access study, 23% of patients had anicteric VOD/SOS at diagnosis; better outcomes occurred in patients with anicteric versus icteric VOD/SOS. This post hoc analysis of a post-approval registry study (NCT03032016; EBMT PASS) evaluated outcomes by bilirubin level at VOD/SOS diagnosis in defibrotide-treated patients.

Method: Defibrotide-treated patients were enrolled from April 2015–July 2018. Investigators diagnosed VOD/SOS using classical/standard criteria and graded severity using clinical expertise.

Results: Overall, 104 defibrotide-treated patients with VOD/SOS post-HCT were analysed (severe VOD/SOS=62; non-severe VOD/SOS=42). Baseline characteristics were similar across subgroups. Among patients with bilirubin ≤2 mg/dL (n=30), 73% and 27% were aged <18 and ≥18 years, respectively. Among patients with severe VOD/SOS, Day 100 post-HCT Kaplan-Meier–estimated survival rates were lower in patients with bilirubin >2 mg/dL (69%) than bilirubin ≤2 mg/dL (90%); Day 100 post-HCT survival was also lower in those with bilirubin >2 mg/dL (86%) versus ≤2 mg/dL (95%) among patients with non-severe disease. VOD/SOS resolution rates were 71% in patients with bilirubin >2 mg/dL versus 80% bilirubin ≤2 mg/dL, among patients with severe VOD/SOS; among patients with non-severe VOD/SOS, the corresponding values were 91% and 100%. Among patients with severe VOD/SOS, serious adverse events (SAEs) of interest occurred in 33% of patients with bilirubin >2 mg/dL and 30% with bilirubin ≤2 mg/dL; corresponding values in patients with non-severe disease were 23% and 20%. The most common categories of SAEs were bleeding and infection.

Conclusion: These data highlight the importance of prompt diagnosis using criteria that recognise VOD/SOS without hyperbilirubinaemia. Early treatment with defibrotide is likely beneficial and the real-world safety profile of defibrotide was consistent with previous studies

H041

The incidence of severe oral mucositis and taste disturbance in patients undergoing different conditioning regimens in haematopoietic stem cell transplantation.

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Title: The incidence of severe oral mucositis and taste disturbance in patients undergoing different conditioning regimens in haematopoietic stem cell transplantation.

Aim: Oral mucositis and taste disturbance are common complications during haematopoietic stem cell transplantation (HSCT). This study aimed to review the incidence of severe mucositis and taste disturbance in patients undergoing different conditioning regimens.

Method: This single-centre retrospective study reviewed daily oral assessment for 467 consecutive patients who received HSCT. Oral care and cryotherapy with melphalan were used. Oral mucositis WHO grade, taste disturbance, use of total parenteral nutrition (TPN) and patient-controlled analgesia (PCA) were collected.

Results: The regimens, graft, patient number (N), melphalan (Mel) dose, total cyclophosphamide (Cy), fludarabine (Flu), and methotrexate (MTX) doses, and the incidence of grade 3-4 (G3-4) oral mucositis are summarised in the table. G3-4 oral mucositis was common in myeloablative TBI based regimens (CyTBI and FluTBI (12Gy) with post-transplant Cy (PTCy)) as well as reduced intensity matched allogeneic protocols (FluMel) and BEAM autologous HSCT. G3-4 oral mucositis was less commonly experienced in reduced intensity haploidentical regimens (MelFluTBI with PTCy), all non-myeloablative regimens (FluCy, FluTBI(2Gy) and FluCyTBI with PTCy) and high dose melphalan (HDM) autologous HSCT. Similarly, TPN and PCA use were common in regimens: CyTBI TPN 67%, PCA 75%; FluTBI (12Gy) with PTCy TPN 75%, PCA 69%; FluMel TPN 42%, PCA 39%; and BEAM TPN18%, PCA 41%. Taste disturbance was common regardless of the conditioning regimens, and overall incidence was 89% (range 71-95%).

Conclusions: Severe oral mucositis was associated with myeloablative TBI, MTX and melphalan in combination with MTX and in BEAM. Use of PTCy was preferable over MTX to prevent oral mucositis. Taste disturbance was common with all regimens.

Regimen	graft	N	TBI (Gy)	Mel (mg/m2)	Cy (mg/kg)	Flu (mg/m2)	MTX (mg/m2)	other	G3-4 (%)
CyTBI (12Gy)	allo	76	12		120		45		71
FluMel	allo	197		120		125	45		43
FluCy	allo	11			120	125	45		9
FluTBI (2Gy)	allo	7	2			90			0
FluTBI (12Gy) with PTCy	haplo	13	12		100	90			46
MelFluTBI (2Gy) with PTCy	haplo	27	2	100	100	160			19
FluCyTBI (2Gy) with PTCy	haplo	7	2		129	150			0
BEAM	auto	34		140				carmustin, etoposide, cytarabine	41
HDM	auto	76		200					26

A comprehensive analysis of the activity and outcomes of autologous stem cell transplantation over a 23-year period in the private sector

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Aim: The Icon Autologous Stem Cell Transplantation (ASCT) clinical and laboratory program was established in 1995. It is one of the few Australasian programs performing ASCTs in the private-sector. Relatively little is known about ASCT outcomes from the private-sector, which varies in care delivery models. We aimed to investigate transplantation activity and survival outcomes from a private-sector program over a 23-year period.

Method: Retrospective, observational study of all adults who underwent ASCT at Icon (Wesley Hospital, WH and Mater Private Hospital, MPH) between 1996-2018. Each patient's medical records were comprehensively reviewed to obtain accurate and timely survival data. We report baseline transplant activity, overall survival (OS), and day-100 and 1-year non-relapse mortality (NRM). Outcomes are benchmarked against ABMTRR.

Results: 1683 ASCTs were performed in 1452 patients (991 WH, 461 MPH), and included 124 salvage and 107 tandem transplants. Between 2014-2018, ASCTs performed at Icon were 34% of all Queensland ASCTs. Median age at transplantation was 60-years. In the last 5-years (2014-2018) 20% of all transplanted patients were ≥70-years, compared to 7% in all other Australasian institutes. The 10-year OS for ASCTs performed between 2001-2018, stratified by disease subtype, is presented in Table 1 and demonstrates favourable survival outcomes at Icon. For the entire cohort, 100-day and 1-year NRM were 1.1% and 1.7% respectively, and for those aged ≥70-years, it was 2.0% and 3.1% respectively. For ASCTs performed between 2014-2018, 100-day and 1-year NRM were 0.8% and 1.4% respectively, compared to 1.6% and 2.7% from ABMTRR.

Conclusion: Icon is the largest contributor to ASCTs in Queensland with excellent OS outcomes and low NRM. The program is inclusive of older patients, utilising ASCT in patients aged ≥70-years and demonstrating low (and acceptable) NRM. This has important implications given the median age of diagnosis with multiple myeloma in Australia is 65-70 years.

The authors acknowledge the essential contribution to this programme of Noor Parker, Laboratory Director 1996-2020

Table 1. Overall survival at 10-years post-ASCT for 1st transplants performed between 2001-2018.

Disease	**Overall Survival at 10-years**	
	Icon	**ABMTRR***
Multiple myeloma	50% (n=619)	36% (n=8322)
DLBCL	60% (n=188)	46% (n=2527)
Follicular lymphoma	72% (n=96)	53% (n=999)
Mantle cell lymphoma	54% (n=73)	48% (n=867)
T and NK-cell lymphoma	42% (n=38)	40% (711)
Hodgkin lymphoma	73% (n=51)	

**Data source: ABMTRR Annual Data Summary, 2019. Courtesy: ABMTR*

H043

Durable remission following salvage therapy for extramedullary relapse of Acute Myeloid Leukaemia (AML) post allogeneic Stem Cell Transplant.

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Aim: To describe a case of durable remission of extramedullary relapse of AML post-allogeneic haematopoietic stem cell transplantation (HSCT) achieved with combined salvage therapy.

Case: The 64-year-old male presented in 2013 with splenomegaly and B-symptoms. He developed mild thrombocytopenia and bone marrow biopsy in 2015 diagnosed myeloproliferative neoplasm/myelodysplastic overlap syndrome with extensive fibrosis. Acute leukaemic transformation to AML occurred in 2016.

He achieved complete remission following induction and consolidation chemotherapy but an abnormal cytogenetic clone persisted. He underwent fludarabine-melphalan-thymoglobulin MUD allogeneic HSCT in June 2017, achieving complete cytogenetic remission and full engraftment. He developed recurring grade II skin and gut graft-versus-host disease (GVHD) requiring therapy.

Results: 12 months post-transplant, multifocal cutaneous abdominal wall sites of extramedullary relapse of AML emerged. Immunosuppression was rapidly weaned, and local radiotherapy administered. The disease progressed rapidly with bilateral testicular involvement and multifocal cutaneous lesions without evidence of bone marrow or CNS involvement. Re-induction chemotherapy and bilateral testicular radiotherapy achieved good partial response followed by consolidation azacitidine and complete remission. He continues his 25th cycle of azacitidine maintenance and remains clinically well with no evidence of active disease.

Conclusion: Relapse following HSCT is associated with a poor response to salvage therapies and overall survival (Tsirigotis *et al.*, 2016). A history of GVHD poses further limitations to treatment options due to risk of additional toxicities. Isolated extramedullary relapse is rare with retrospective studies suggesting marginally better overall survival than marrow relapse (Yuda *et al.*, 2019). Multimodal salvage therapy that included chemotherapy, radiation, withdrawal of immunosuppression, azacitidine consolidation and maintenance was successful in achieving durable remission in this case. Although the prognostic significance of his initial abnormal cytogenetics with an isodicentric chromosome 20 was uncertain (Saunders *et al.*, 2005), his case history adds further experience to be associated with this finding.

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H044

Associations with early non-relapse mortality post allogeneic stem cell transplant.

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Aim:
Whilst the haematopoietic cell transplantation comorbidity index (HCT-CI) has been used to predict overall non-relapse mortality there is limited information regarding associations with early non-relapse mortality (NRM) defined as non-relapse related death within the 1st 60 days of transplantation. We evaluated our local transplant cohort to identify associations with early NRM.
Method:
This was a retrospective case control study of patients who received an allogeneic stem cell transplant (alloSCT) from 2008-2018 at our centre. Patients who experienced early NRM were compared to a randomly selected cohort matched for age and disease who survived to D100 without relapse. Variables assessed included time from diagnosis to transplant (TDTT), complicated pre-transplant infections (defined as fungal, viral, or infection requiring extended antibiotic or surgical therapy), prior solid organ malignancy, ≥3 lines of chemotherapy or CR2 for AML (prior treatment intensity) and an antecedent haematologic condition (AHC) different from primary indication for allogeneic transplant were evaluated as potential associations with early NRM.
Results:
Thirty-three patients, with early NRM and 163 suitable comparators were included in the final analysis. Results of univariate analysis were as follows: TDTT [OR 1.0; CI 1.0-1.0; p=0.06], infection [OR 1.90; CI 0.58-5.42; p= 0.25], prior solid organ malignancy [OR 1.26; CI 0.27-4.26; p=0.73], prior treatment intensity [OR 1.83; CI 0.79-4.07; p=0.15] and AHC [OR 3.08; CI 1.29-7.15; p=0.005].

Conclusion:
AHC was significantly associated with early NRM in our cohort and may identify patients with a lower tolerance of alloSCT.

H045

Successful Management of Disseminated Fusariosis in Two Patients with Acute Myeloid Leukaemia Proceeding to Allogeneic Transplantation.

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Aim: Disseminated *fusarium* infection is associated with high mortality in immunocompromised patients. Most case reports in the literature outline poor clinical outcomes associated with disseminated *fusarium* infection in the context of acute myeloid leukaemia (AML)(Dehal, 2019; Fujishita, 2020; Narayanan, 2016). There are very few case reports of patients with disseminated *fusarium* infection with AML proceeding to successful allogeneic haemopoietic cell transplantation (HCT) (Ichikawa, 2020; Sheela, 2017). This report outlines the management and outcome of two patients in our centre who developed disseminated *fusarium* during AML therapy prior to successful HCT.

Method: Two cases managed at Royal North Shore Hospital in Sydney, Australia are described. Cases were female patients aged 31 (patient 1) and 68 years (patient 2) with primary refractory AML, with residual disease on bone marrow biopsy after 7:3 induction chemotherapy. Following re-induction, both patients developed disseminated *fusarium solani* infection despite prophylactic posaconazole. These patients were managed with intra-vitreal antifungals, surgical debridement, amphotericin and voriconazole prior to HCT. Patient 2 also received concomitant terbinafine. Patient 2 was changed to single agent isavuconazole one week prior to HCT conditioning due to drug-induced renal impairment. She recommenced amphotericin, voriconazole and terbinafine day+4 post HCT.

Results: Both cases proceeded to successful HCT despite preceding *fusarium* infection. Patient 1 remains in remission from AML and off all immunosuppression 641 days post-transplant. This patient continues on liposomal amphotericin B while awaiting completion of a staged knee replacement due to joint involvement by *fusarium*. Patient 2 ceased *fusarium* directed antifungal therapy two months after transplant. This patient relapsed with AML 278 days after HCT. She developed localised *fusarium* discitis 500 days post-transplant and was managed with surgical debridement and voriconazole indefinitely.

Conclusion: These two cases outline management of a complex fungal infection pre-HCT. These cases may assist HCT physicians develop strategies that can permit successful HCT in patients with AML and disseminated *fusarium* infection.

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H046

The experience of a therapeutic platelet transfusion strategy in autologous stem cell transplant (ASCT) at Gold Coast University Hospital (GCUH)

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Aim: To demonstrate the safety and feasibility of a therapeutic platelet transfusion strategy in ASCTs.

Method: Single centre, retrospective review on ASCT patients from January 2017-December 2020. A minimum of 2- 2.5x10^6 stem-cells/kg was required for ASCT. Conditioning regimens included Mel200/140, BEAM or BCNU-Thiotepa. Patients were admitted for ASCT and received prophylactic antimicrobials until engraftment. Amyloid ASCTs were excluded.

The prophylactic era (PE) was 2017-2018; patients received platelets to maintain platelets >10-20x10^9. The therapeutic era (TE) was 2019-2020, whereby a therapeutic platelet strategy was implemented. Suitable patients were identified using a questionnaire which excluded those with increased bleeding risk. Patients assigned the therapeutic strategy were transfused platelets for bleeding or clinical concern.

Statistical analysis was performed on STATA v15.1. Platelet recovery was defined as unsupported platelet count >20x10^9. Bleeding was defined by WHO bleeding score, considering chemotherapy associated anaemia.

Results: There were 142 ASCTs in 136 patients in the entire cohort. Median age 57.5 (range 17-70), 61% male, 60% myeloma, 36% lymphoma and 2% solid tumour. Conditioning was Mel200 60%, BEAM 34%, BCNU-Thiotepa 3%, other 3%. In the PE (74 ASCTs); 10% (8/74) did not require a platelet transfusion. 10% received no blood products. Minor bleeding episodes was 8 in 7 patients; major bleeding was 0. In the TE, (68 ASCTs), 90% (61/68) were assessed as safe for the therapeutic strategy; 51% received no platelets, 42% received no blood products. Minor bleeding episodes was 18 in 13 patients; major bleeding was 0. 211 platelet transfusions occurred in 74 ASCTs compared to 77 in 68 ASCTs in the TE (P<0.0001). Minor bleeding was increased in TE(P< 0.0001), but not major bleeding, RBC transfusion, ICU admission or length of stay.

Conclusion: A therapeutic platelet transfusion strategy is safe in ASCT and is applicable to most patients, resulting in substantial reduction in platelet usage.

H047

A retrospective audit of early discharge (day +1) following autologous stem cell transplantation

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Aim: To determine the safety of early discharge and outpatient management of the neutropenic period following autologous stem cell transplantation, compared to completely inpatient treatment at our centre.

Method: A retrospective review of records from all patients who received ASCT between January 2010 and December 2017 at our centre was performed. Data on transplantation and complications within 30 days of conditioning chemotherapy was collected.

Results: 244 transplants were conducted in the study period. 8 were excluded due to insufficient data. 132 transplants were for the treatment of myeloma, 69 non-Hodgkin lymphoma, 20 Hodgkin lymphoma, and 13 non-haematologic malignancies. 97 patients were discharged on day +1, and 139 transplants were completely inpatient. Median nights in hospital was 9 (early discharge) versus 19 (inpatient). Early discharge was associated with fewer red blood cell transfuions (1 vs 2, p0.021) and fewer platelet transfusions (2 vs 3, p0.001). 44 patients (45%) were re-admitted following early discharge, 36 of them (37%) for fever. By comparison, 100% of completely inpatient transplants had documented fevers. There was no difference in the rate of positive blood cultures or other microbiological investigations. Only one patient died during the study period, and there was no difference in the need for ICU admission.

Conclusion: Early discharge and outpatient management following autologous stem cell transplantation is safe and reduces hospital bed days significantly. The incidence of documented fever was substantially lower in the early discharge population. Blood product usage was also reduced. This data has informed the development of a Completely Outpatient Autologous Stem Cell Transplant (COASCT) program at our centre.

H048

Acute kidney injury in patients receiving high-dose etoposide phosphate prior to hematopoietic stem cell transplant is associated with high body mass index – a multisite retrospective analysis.

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Aim: We observed several cases of acute kidney injury (AKI - defined as doubling in serum creatinine) within 48 hours of high-dose etoposide phosphate (EP – defined as either 60mg/kg or 800mg/m^2) administration as part of conditioning for autologous and allogeneic stem cell transplantation (SCT). Previous reports suggest that the mechanism may be osmotic nephrosis due to Dextran-40 used in EP[1]. This study aims to determine risk factors associated with this phenomenon.

Methods: We analysed data from a retrospective cohort from three tertiary centres. The characteristics of patients with AKI (age, conditioning chemotherapy, disease subtype, body mass index (BMI), baseline creatinine) were compared to those without AKI using the chi-square statistical test. Comparison of mean and median values were conducted using an independent samples t-test of two-sample Wilcoxon rank-sum test.

Results: Eight patients of 124 who received EP as conditioning prior to SCT developed clinically significant AKI within 48 hours of EP administration. This cohort had a higher BMI (median (range) 31.6 (20.9–44.7) vs. 25.5 (19.4–45.6), p=0.002) and a higher dose of EP (median (range) 6021mg (4200–9480) vs 4620mg (1216–8280), p=0.001) *(Table 1)*. There was no difference between the two groups in age, baseline creatinine (*Table 1)*, disease subtype nor conditioning chemotherapy. Complications in the AKI cohort included death (n=1), dialysis (n=1), omission (n=1) or delay (n=1) of subsequent chemotherapy. 7 of 8 patients achieved full renal recovery.

Conclusion: AKI developing early post administration of EP is associated with a higher BMI and a corresponding higher dose. These results should prompt consideration of dose-reduction (capping based on BMI or weight) for obese patients receiving high-dose EP to prevent a significant impact on delivery of potentially curative therapy

Table 2: Patient's characteristics

Characteristic	AKI status: No (n = 116)	AKI status: Yes (n = 8)	Total (n = 124)	p-value
Age, (years)				
Mean (SD)	51.4 (16.4)	44.6 (14.7)	51.0 (16.4)	
Median [range]	57.5 [15.0 - 76.0]	45.0 [23.0 - 64.0]	54.5 [15.0 - 76.0]	0.257
IQR	36.8 - 65.0	36.2 - 53.8	36.8 - 64.0	
Body mass index				
Mean (SD)	26.6 (4.7)	32.2 (6.8)	26.9 (5.0)	
Median [range]	25.5 [19.4 - 45.6]	31.6 [20.9 - 44.7]	25.7 [19.4 - 45.6]	0.002
IQR	23.7 - 28.3	29.5 - 34.5	23.8 - 28.9	
Dose of etoposide based on dosing with actual body weight, mg				
Mean (SD)	4623.7 (1181.2)	6105.0 (1636.8)	4719.3 (1261.2)	
Median [range]	4620.0 [1216.0 - 8280.0]	6021.0 [4200.0 - 9480.0]	4626.0 [1216.0 - 9480.0]	0.001
IQR	4065.0 - 5286.0	5002.5 - 6591.0	4080.0 - 5406.0	
Baseline creatinine, umol/L				
Mean (SD)	70.6 (15.0)	73.1 (20.4)	70.8 (15.3)	
Median [range]	68.0 [38.0 - 121.0]	69.0 [50.0 - 108.0]	68.0 [38.0 - 121.0]	0.655
IQR	61.0 - 77.0	59.8 - 87.5	61.0 - 78.5	

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H049

Prior skin cancer and age predict skin cancer development following allogeneic haematopoietic stem cell transplant

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Aim: Allogeneic haematopoietic stem cell transplant (HSCT) confers a lifetime increased risk of secondary malignancies such as skin cancer. This is relevant in Australia, where melanoma, squamous cell carcinoma and basal cell carcinoma are endemic in the general population. Although studies have suggested chronic GVHD, conditioning regimen and voriconazole usage as possible contributors to skin cancer development, few have assessed the potential impact of pre-HSCT risk factors. We conducted a retrospective single-centre study to assess incidence and potential risk factors for skin cancer following HSCT.

Method: Adult HSCT recipients between 2014-18 were identified from an institutional database. At our institution, all patients routinely undertake formal dermatological assessment pre-HSCT and post-HSCT. Patient data obtained by chart review included: demographics, haematologic disease, conditioning, incidence of acute and chronic GVHD, history of pre-HSCT skin cancer, incidence of post-HSCT skin cancer, and survival. Statistical analysis was performed using a stepwise logistic regression model for multivariate analysis of co-variables that were significantly associated with post-HSCT skin cancer.

Results: 476 patients were included. Of those, 126 (26%) had a prior history of skin cancer (19 melanoma, 148 NMSC). Post-HSCT, 111 (23%) patients developed skin cancer within two years (8 melanoma, 78 SCC, 104 BCC, 104 IEC). Of these, 65 patients (61%) had a pre-HSCT history. Univariate and multivariate analyses identified pre-HSCT skin cancer (OR 8.65, $p<0.001$) and increased age (OR 6.0, $p<0.001$) as predictive for post-HSCT skin cancer development, whereas severe cutaneous aGVHD appeared protective (OR 0.39, $p=0.02$). Conditioning and cGVHD did not significantly impact post-HSCT skin cancer incidence.

Conclusion: This is the first reported study to examine pre-HSCT skin cancer as a risk factor. Prior history and age are the most significant risk factors for post-HSCT skin cancer, regardless of other variables. Our study supports regular post-HSCT skin cancer screening programs and sun safety.

H050

Ibrutinib in relapsed/refractory chronic lymphocytic leukaemia: interim analysis of outcomes on a Named Patient Program from the Lymphoma and Related Diseases Registry

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Aim: Ibrutinib is now an established therapy option for both treatment-naïve and relapsed/refractory chronic lymphocytic leukaemia (CLL). This retrospective Registry study describes outcomes of a historical cohort of Australian patients treated with ibrutinib for relapsed/refractory CLL on a 'Named Patient Program' (NPP).

Method: Patients treated with ibrutinib were identified from 13 Australian centres via a centralized, de-identified database, the Lymphoma And Related Diseases Registry (LaRDR). Baseline characteristics, survival outcomes and adverse events were compared to published randomized data.

Results: Between 1st December 2014 and 30th November 2017, 1015 patients, whose demographics have been previously described [1], accessed ibrutinib on the NPP. Of an estimated 245 LaRDR-registered patients, 76 were identified for this analysis. 68% were male, and median age at diagnosis was 64.4 years. Cytogenetic information was only available in 25 (32%) patients, of whom 7 (28%) had del(17p) or *TP53* mutations. The median prior lines of therapy was 2 (range 1-7), 20% had received □3 lines of therapy, and 50% had failed purine analogue therapy. With a median follow-up of 18 months from commencement of ibrutinib therapy, Kaplan-Meier estimated median progression-free survival (PFS) was 36 months (95% CI 15.6-42) and overall survival (OS) was 55.2 months (95% CI 38.4 – not reached). During follow-up, 11 (15%) patients experienced Richter transformation, and 14 (18%) experienced a secondary malignancy including 7 (9%) non-melanomatous skin cancers and 3 (4%) melanoma.

Conclusion: Compared with data from international trials [2], this cohort of real-world Australian relapsed/refractory CLL patients had similar age and median lines of therapy, but lower PFS and OS of 36 and 55.2 months respectively. A higher-than-expected incidence of Richter transformation may reflect poorer disease biology, despite missing information regarding molecular profile. Given its importance in therapy selection, low uptake of cytogenetic and molecular testing is noted as an area for improvement.
Study funded by Janssen.

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H051

Ibrutinib protects T cells in patients with CLL from proliferation-induced senescence.

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Aim: The development of Bruton tyrosine kinase inhibitors (BTKi) for the treatment of chronic lymphocytic leukaemia (CLL) has provided a highly effective alternative to conventional chemotherapy. Some studies have shown that BTKi can improve T cell immunity in patients despite *in vitro* analyses suggesting an immunosuppressive effect of BTKi on T cell function. In this study, we examined both the *in vitro* effect and long-term *in vivo* effect of two clinically available BTKi, ibrutinib and zanubrutinib.

Method: CLL patients refractory to previous treatment were treated with single-agent ibrutinib under compassionate access, or zanubrutinib under a Phase I clinical trial at the Peter MacCallum Cancer Centre and The Royal Melbourne Hospital. Baseline blood samples were collected prior to treatment, and long-term treatment samples were collected after 12 months on zanubrutinib therapy (n=8), and between 12-24 months on ibrutinib therapy (n=7). Age-matched healthy donor (n=7) samples were used in *ex vivo* and *in vitro* analyses compared with baseline and long-term treatment CLL samples, including T cell proliferation, degranulation and cytokine release assays.

Results: Long-term BTKi treatment normalised lymphocyte subset frequency, reduced PD-1 expression and improved cytokine release from T cells. T cells from patients taken prior to BTKi therapy showed an abnormal hyper-proliferation pattern typical of senescent T cells, which was normalised by long-term BTKi treatment. Furthermore, BTKi therapy resulted in reduced expression of the T cell exhaustion markers PD-1, TIM3 and LAG3 in late generations of T cells undergoing proliferation. Collectively, these findings indicate that there are critical differences between the *in vitro* effects of BTKi on T cell function and the effects derived from long-term BTKi exposure *in vivo*.

Conclusion: Long-term exposure to BTKi, particularly ibrutinib, resulted in improved T cell fitness in part due to suppressing the abnormal hyper-proliferation of CLL T cells and the associated over-expression of T cell senescence markers.

H052

First-in-human study of lisaftoclax (APG-2575), a novel BCL-2 inhibitor (BCL-2i), in patients (pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) and other hematologic malignancies (HMs)

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Aim: APG-2575 has preliminary activity against HMs. The primary aim of this phase 1 study is to evaluate the safety of this BCL-2i, including maximum tolerated dose (MTD). Secondary objectives are to assess pharmacokinetics and initial antitumor effects.

Method: This phase 1 study (NCT03537482) enrolled Australian and US patients with R/R HMs and no prior BCL-2i treatment. APG-2575 (20-1,200 mg/day) was administered orally in a 28-day cycle, and patients with CLL or intermediate-to-high risk of tumor lysis syndrome (TLS) were initiated on a daily dose ramp-up schedule.

Results: On April 15, 2021, the study had enrolled 36 heavily pretreated patients with diagnoses of R/R CLL or SLL (n = 15), MM (n = 6), FL or WM (n =5 each), and either AML, MDS, MCL, DLBCL, or hairy-cell leukemia (n = 1 each). No MTD or TLS was observed. Systemic exposures were dose dependent (elimination half-life 4-5 hours). Treatment-related adverse events in all patients included fatigue in 27.8%, neutropenia (22.2%), diarrhea (19.4%), anemia (16.7%), and constipation or nausea (11.1% each). Grade ≥ 3 events were infrequent (neutropenia 13.9%; nausea or reduced platelets 5.6%). The ORR was 80% based on partial responses (PRs) in 12 of 15 evaluable R/R CLL/SLL pts, and APG-2575 showed activity across multiple HMs (Figure). Representative patient data included rapid and sharp reductions in absolute lymphocyte count, as well as a durable PR with an 89% reduction in portocaval lymph node dimensions by Cycle 3 Day 1 (and 90% by C5D1) and enhanced bone marrow scans at C5D1.

Conclusion: APG-2575 was well tolerated, with no MTD or TLS and an ORR of 80% in patients with R/R CLL or SLL. APG-2575 holds promise as a potential treatment alternative for patients with R/R HMs, with a shorter daily (vs weekly) ramp-up that may be convenient for patients.

H053

VEXAS syndrome associated with low-grade B-cell lymphoproliferative disorder

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Background: VEXAS (Vacuoles, E1 Enzyme, X-linked, Autoinflammatory, Somatic) syndrome is a recently described X-linked adult-onset inflammatory disorder caused by somatic codon 41 (p.Met41) mutations in *UBA1,* which encodes a ubiquitin-like modifier activating enzyme gene (1). Common manifestations include pyrexia, chondritis, cutaneous vasculitis and pulmonary infiltrates (3,4). Described haematological involvement includes macrocytic anaemia, secondary myelodysplastic syndrome with cytoplasmic vacuoles in myeloid precursors, and venous thromboembolism (3,5).
Case Report: We describe the clinical progress of a 66-year-old male with indolent CLL for 6 years. He had comorbid, difficult to control, inflammatory arthritis necessitating use of various disease modifying drugs.

In 2019, he developed fevers, night sweats, skin rash, chondritis and recurrent orbital cellulitis. He became transfusion dependent in early 2020, with raised inflammatory markers. He had stable mild lymphocytosis with trace levels of paraprotein. Bone marrow biopsy was nondiagnostic with reactive changes, minor dysplasia and lymphoid infiltrate. Due to his ongoing constellation of symptoms, a decision was taken to treat his presumed low grade non-hodgkin lymphoma with rituximab and bendamustine. His chemotherapy was ceased after the third cycle due to recurrent infections, frailty and confirmed remission on repeat bone marrow biopsy. His inflammatory symptoms improved initially, however, his functional decline continued with transfusion dependence (possible myelodysplasia), recurrent deep vein thrombosis, C3 glomerulonephritis and recurrent orbital cellulitis with persistently raised inflammatory markers. He was managed with corticosteroids, mycophenolate sodium, transfusions and anticoagulants.
Following the description of VEXAS syndrome, and noting that previous bone marrow biopsies had shown vacuolation of myeloid precursors, we carried out Sanger sequencing of the *UBA1* gene identifying a c.121A>G mutation causing p.Met41Val mutation.

Conclusion: VEXAS should be considered in cases where profound inflammation coincides with evidence of likely myelodysplastic syndrome even if there is a pre-existing haematological diagnosis.

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H054

Understanding ibrutinib utilisation and duration on treatment in Australia for patients with relapsed or refractory chronic lymphocytic leukaemia

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Aim: To analyse usage trends and duration on treatment for patients with relapsed/refractory chronic lymphocytic leukaemia (R/R CLL) on Pharmaceutical Benefits Scheme (PBS) reimbursed ibrutinib.

Method: A retrospective cohort analysis was conducted using Australian Department of Human Services PBS data, drawn from a randomly selected sample comprising 10% of all PBS prescriptions from December 2017 to September 2020 (a validated method of representative sampling). PBS indications identified ibrutinib scripts for R/R CLL. Utilisation was considered persistent until 6-months without a script. Duration on treatment was evaluated using Kaplan-Meier curves. Comparisons to published Phase 3 RESONATE trial results were made using log-rank tests.

Results: The 10% sample yielded 216 patients prescribed ibrutinib for R/R CLL since listed on the Australian PBS. The median age was 75 years, 67.7% were male, and most (59.8%) were at first relapse. Median duration on PBS treatment had not been reached and 69% of patients were still on therapy 34 months after starting treatment. Compared to the Phase 3 RESONATE trial, PBS patients were older (75 vs 67 years), more likely to receive ibrutinib earlier in the treatment pathway, but had significantly longer duration on treatment (HR 0.61, p=0.01, 95% CI=0.42-0.88). Co-medication for other conditions such as cardiovascular disease was common, with only 24.2% solely taking PBS ibrutinib therapy.

Conclusion:
The PBS accounted for virtually all national ibrutinib use in R/R CLL in this period. After almost 3 years, duration on treatment with PBS ibrutinib was significantly longer than the Phase 3 RESONATE cohort, despite significantly older age and frequent co-medication use. Treatment at first relapse was more frequent, consistent with contemporaneous R/R CLL therapy access and trial data. Median duration on PBS treatment has yet to be reached, demonstrating ibrutinib safety, efficacy, patient compliance, and consistent with confidence of usage and clinical trial data.

H055

Venetoclax-Rituximab treatment outcomes in Richter's transformation of chronic lymphocytic leukaemia – a case series

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Introduction: Richter's transformation (RT) occurs in 5-15% of CLL patients[1,2], 90% of which progress to DLBCL[1]. Prognosis for RT is poor with median OS ranging from 5-24 months depending on clonality. Treatment currently mirrors that of treatments for DLBCL de novo with RCHOP being the most widely used regime, with little available treatment if refractory[1,2,3]. No studies have looked at the combination of Venetoclax-rituximab (VR) which has shown good evidence in refractory CLL[4]. Case studies have shown that Venetoclax monotherapy has a partial response in patients with RT[5].

Case Series: Three patients were identified across 2 QLD health sites who had been treated with VR (based on MURANO dosing) with RT, all of which had a DLBCL subtype which was resistant to standard therapy. All three patients showed partial or complete response to therapy and achieved reasonable PFS which exceeded prognostic expectations prior to treatment. Side effects experienced by patients in this study were predominantly related to cytopenia's in accordance with previous trials.

Discussion: Patients with RT have a poor prognosis. On average only 50-60% of patients respond to conventional therapy such as RCHOP and for those with refractory disease there are few options[3]. This small study has shown that the use of VR in RT in select cases is able to achieve disease control and achieve reasonable PFS. In one case we observed complete remission of disease. Side effects were in keeping with previous studies. No episodes of tumour lysis syndrome were recorded.

Conclusion: CLL with RT is an aggressive disease with generally poor outcomes. Effective therapy for this challenging population is clearly an unmet need. This limited case series highlights favourable outcomes of Venetoclax/Rituximab in a heavily pre-treated population. Ongoing trials are required to further assess its efficacy in combination with chemo-immunotherapy.

H056

Second Primary Malignancies in Chronic Lymphocytic Leukaemia: Skin Cancer, Solid Organ Malignancy, Second Haematological Malignancy, and Richter's Syndrome, A Comprehensive Analysis at a Single Institution.

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Aim: To comprehensively document the incidence of all forms of second primary malignancy (SPM) including skin cancer (SC), solid organ malignancy (SOM), second haematological malignancy (SHM), and Richter's Syndrome (RS), in patients with chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and monoclonal B-lymphocytosis (MBL) in a single institution cohort.

Method: Data was obtained from patients (570) with CLL, SLL or MBL at Royal North Shore Hospital, Sydney, with a minimum of 1 and up to 39 years of follow-up. We separately analysed the incidence of SC, SOM, SHM and RS for patients with CLL/SLL or MBL. Statistics were evaluated using Chi-square test, Kaplan–Meier curves and Hazard Ratios by the Mantel-Haenszel method.

Results: Of the 517 CLL/SLL patients, 122 had SC (23.6%), 103 had SOM (19.9%) and 30 had a SHM (5.8%), not including 31 with RS (6.0%). Melanoma accounted for 30.3% of SC, and squamous cell carcinoma (SCC), including 8 metastatic SCCs, constituted two-thirds of the non-melanoma skin cancer, 1.8 times more than basal cell carcinoma (BCC), a reversal of the typical BCC:SCC ratio. The most common SOM were prostate (6.4%) and breast (4.5%) cancers. SHM included 7 acute myeloid leukemia and 5 myelodysplasia of whom 75% had prior CLL therapy. Myeloproliferative neoplasms occurred in 6, and a second low-grade lymphoproliferative or plasma cell disorder in 12. The incidence of RS was 6.0%. The 53 MBL patients also had a higher incidence of SPM with 17% SC, 13.2% SOM and 3.8% RS.

Conclusion: SPM are a major health burden occurring in 44.9% of CLL, well above the expected population incidence and, apart from SC, associated with significantly reduced survival. Dramatic improvements in CLL treatment and survival have occurred with immunochemotherapy and targeted therapies but mitigating SPM burden will be important to sustain further progress.

H057

Pirtobrutinib (LOXO-305), a next generation, highly selective, non-covalent BTK inhibitor in previously treated CLL/SLL: Results from the Phase 1/2 BRUIN study

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Aim: To evaluate the safety and efficacy of pirtobrutinib in previously treated CLL/SLL.

Method: The BRUIN trial is a multicenter phase 1/2 trial (NCT03740529) evaluating oral pirtobrutinib in pretreated pts with advanced B-cell malignancies. The primary endpoint was MTD/RP2D identification.

Results: As of 27 September 2020, 323 pts with B-cell malignancies (170 CLL/SLL, 61 MCL, 26 WM, and 66 other B-cell lymphomas) were treated on 7 dose levels (25-300mg QD). Pirtobrutinib demonstrated high oral exposures, with doses ≥100mg QD exceeding the BTK IC_{90} for the entirety of the dosing interval. No DLTs occurred. The only treatment-emergent adverse events regardless of attribution or grade seen in ≥10% of pts (n=323) were fatigue (20%), diarrhea (17%) and contusion (13%). A RP2D of 200mg QD was selected for future studies. The ORR (per iwCLL 2018) was 63%, with 69 PRs, 19 PR-Ls, 45 SDs, 1 PD, and 5 discontinued prior to first response assessment. Responses deepened over time among pts with ≥10 months of follow-up (n=29; 86% ORR). ORR was not influenced by the reason for prior BTKi discontinuation (i.e., progression vs intolerance), or other classes of prior therapy received (including a covalent BTK and a BCL2 inhibitor). The longest followed responding pt continues on treatment for 17.8+ months.

Conclusion: Pirtobrutinib demonstrated promising efficacy in pretreated CLL/SLL pts, was well tolerated and exhibited a wide therapeutic index.

H058

A case of profound haemolytic anaemia on nivolumab

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Warm autoimmune haemolytic anaemia is a well-recognised but rare complication of chronic lymphocytic leukaemia. We present a case study of a 78 year old male who initially presented with left sided acute abdominal pain. His background is metastatic squamous cell carcinoma currently stable on nivolumab monotherapy after previous chemoradiotherapy and surgical resections and chronic lymphocytic leukaemia (del13q mutation) previously well controlled on ibrutinib but recently self-ceased due to impetigo and neurological intolerance. Blood tests incidentally showed a profound macrocytic anaemia with a haemoglobin of 47 grams per litre. On further questioning there was no clinical evidence of bleeding. Further investigations confirmed a diagnosis of warm autoimmune haemolytic anaemia with a low haptoglobin, reticulocytosis, raised lactate dehydrogenase, raised bilirubin and direct antiglobulin test positive for IgG. CT scan showed widespread lymphadenopathy and splenomegaly consistent with progression of chronic lymphocytic leukaemia. He was commenced on high dose prednisone as a bridge to restarting ibrutinib along with being given packed red blood cell transfusion with marked improvement in his abdominal pain and anaemia. His nivolumab was briefly suspended during this treatment. On outpatient review, our case has remained well on maintenance ibrutinib with successful weaning off prednisone and restarting regular nivolumab. His most recent haemoglobin is 120 grams per litre and he has had normalisation of all haemolysis markers. Progress CT scanning has showed regression of all previously noted lymphadenopathy and splenomegaly. He is tolerating his current dose of ibrutinib despite mild neurological side effects. This case demonstrates the importance of rapid identification of causes of anaemia in the complex clinical scenario of multiple malignancies as well as the positive outcomes that can be achieved with effective immunosuppression.

H059

Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naïve Chronic Lymphocytic Leukemia: ELEVATE-TN 4-Year Follow-up

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Aim: Early results from ELEVATE-TN (NCT02475681) at a median follow-up of 28.3 mo demonstrated superior efficacy of acalabrutinib (A) ± obinutuzumab (O) compared with O + chlorambucil (Clb) in patients (pts) with treatment-naïve (TN) chronic lymphocytic leukemia (CLL) (Sharman et al. Lancet 2020;395:1278-91). Results from a 4-year update are reported here.

Method: Pts received A±O or O+Clb. Crossover to A monotherapy was permitted in pts who progressed on O+Clb. Investigator-assessed (INV) progression-free survival (PFS), INV overall response rate (ORR), overall survival (OS), and safety were evaluated.

Results: 535 pts (A+O, n=179; A, n=179; O+Clb, n=177) were randomized with a median age of 70 y; 63% had unmutated IGHV and 9% del(17p). At a median follow-up of 46.9 mo (range, 0.0–59.4; data cutoff: Sept 11, 2020), the median PFS was not reached (NR) for A+O and A vs 27.8 mo for O+Clb (both P<0.0001). Estimated 48-mo PFS rates were 87% for A+O, 78% for A, and 25% for O+Clb. Median OS was NR in any treatment arm; estimated 48-mo OS rates were 93% (A+O), 88% (A), and 88% (O+Clb). ORR was significantly higher with A+O (96.1%; 95% CI 92.1–98.1) vs O+Clb (82.5%; 95% CI 76.2–87.4; P<0.0001); ORR with A was 89.9% (95% CI 84.7–93.5; P=0.035 vs O+Clb). Complete response/complete response with incomplete hematologic recovery (CR/CRi) rates were higher with A+O (26.8%/3.9%) vs O+Clb (12.4%/0.6%); 10.6%/0.6% had CR/CRi with A. Overall treatment discontinuation rates were 25.1% (A+O), 30.7% (A), and 22.6% (O+Clb); the most common reasons were AEs (12.8%, 12.3%, 14.7%, respectively) and progressive disease (4.5%, 7.8%, 1.7%).

Conclusion: With a median follow-up of 46.9 mo (~4y), the efficacy and safety of A+O and A monotherapy was maintained, with an increase in CR since the interim analysis (from 21% to 27% [A+O] and from 7% to 11% [A]) and low rates of discontinuation.

H060

Does abnormal lymphoblast populations at diagnosis of chronic myeloid leukaemia predict increased risk of blast crisis? A case report and review of the literature.

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Title: Does abnormal lymphoblast populations at diagnosis of chronic myeloid leukaemia predict increased risk of blast crisis? A case report and review of the literature.

Aim: We report an unusual case of chronic myeloid leukaemia in chronic phase (CML-CP) with a small abnormal lymphoblast population (ABLP) at diagnosis, which progressed to blast phase on tyrosine kinase inhibitor (TKI) therapy, and provide a review of the literature.

Method: In our community-based laboratory 10-colour flow cytometry is performed on all bone marrow aspirates. This case was identified through routine analysis.

Case report and literature review: A 73-year-old lady presented with neutrophilia ($10.5x10^9$/L) and basophilia ($1.2x10^9$/L) on routine blood tests. BCR/ABL1 dual colour FISH detected the BCR-ABL1 gene fusion and bone marrow aspirate and trephine confirmed CML-CP. Flow cytometry on the bone marrow aspirate identified an ALBP comprising 0.2% of all cells with a phenotype of CD45weak/+, CD34weak/+ CD19+/++, CD10++, CD38weak/+, CD9++, CD20+(variable), SmIg-.

The patient commenced imatinib, achieving a major molecular response (MMR). Four years later she progressed with abrupt lymphoblast crisis. The phenotype of the lymphoblasts was similar, but not identical, to those detected at diagnosis. She commenced treatment with dexamethasone, vincristine and dasatinib, again achieving MMR.

We identified 18 cases of CML-CP with an ALBP in the literature [1-4]. The incidence of ALBP in CML-CP in these studies was 6-11%. The rates of transformation varied between publications but pooling the papers available, the number of patients transforming to blast phase is significantly higher than that expected in patients treated with TKI, with 6/18 (33%) developing myeloid or lymphoid blast crisis within follow-up of 1-67 months [5].

Conclusion: Flow cytometry is not always performed in patients with CML-CP, however should be considered on diagnostic bone marrows in such patients as it may help identify those who may be at increased risk of progressing to blast crisis in the era of TKI therapy.

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H061

Novel BCR-ABL1 tyrosine kinase inhibitor (TKI) HQP1351 (olverembatinib) is efficacious and well tolerated in patients with T315I-mutated chronic myeloid leukemia (CML): results of pivotal (phase 2) trials

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Aim: HQP1351 is a third-generation TKI with potent activity against wild-type and mutant BCR-ABL1. Preliminary evidence suggests that HQP1351 confers antileukemic activity irrespective of genotype, including the T315I and compound mutations which can complicate CML management. The primary purpose of this study is to evaluate the efficacy of HQP1351 as assessed by major cytogenetic response (MCyR) in patients with chronic-phase CML (CP-CML) and major hematologic response (MHR) in those with accelerated-phase CML (AP-CML). Secondary endpoints include safety and tolerability.

Method: TKI resistant adults with CP-CML (n = 41; NCT03883087) or AP-CML (n = 23; NCT03883100) and T315I mutations are being enrolled into two single-arm, multicenter, open-label pivotal trials. HQP1351 40 mg is administered orally on alternate days for 28 consecutive days per cycle over 24 months.

Results: Median (range) ages were 47 (22-70) years in patients with CP-CML and 41 (21-74) with AP-CML. A total of 78% of patients had received 2 or more lines of TKIs. Across a median follow-up of approximately 8 months, the mean 3-month progression-free survival (PFS) was 100% and the 6-month PFS approximately 96% in both CP-CML and AP-CML patients. Most individuals experienced MCyR, CHR, and other endpoints, including 76% of CP-CML patients with MCyR and 78% of AP-CML patients with MHR (**Figure**). HQP1351 was well tolerated. Frequent treatment-related adverse events (any grade; grade 3-4) in CP-CML patients included thrombocytopenia (65.9%; 48.8%), anemia (48.8%; 24.4%), leukopenia (46.3%; 12.2%), and neutropenia (36.6%; 19.5%). Corresponding values (any grade; grade 3-4; serious AE) in AP-CML patients included thrombocytopenia (73.9%; 52.2%; 17.4%), anemia (65.2%; 39.1%; 13.0%), leukopenia (56.5%; 30.4%; 0), and neutropenia (26.1%; 21.7%; 0). Treatment-related changes in skin pigmentation occurred in both CP-CML (53.7%) and AP-CML (69.6%) patients.

Conclusion: HQP1351 is efficacious in heavily TKI pretreated patients who have T315I-mutated CML and is well tolerated.

H062

Burkitt Lymphoma: A retrospective review of demographics and outcomes for patients treated at a single tertiary centre.

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Aim: Non-endemic Burkitt lymphoma is a rare, clinically aggressive B-cell-derived malignancy, making prospective randomised trials difficult to conduct. Retrospective analyses provide a surrogate measure of identifying clinically significant outcomes linked to different immuno-chemotherapy regimes. The primary aim of this study was to record demographic, treatment and overall survival data for newly diagnosed adult Burkitt Lymphoma patients at a single tertiary centre and compare it with larger multi-centre analyses[1]. Secondary aims included comparing outcomes for rural and metropolitan patients in order to identify barriers to delivering care.

Method:
Digital medical records were accessed for 19 patients at Fiona Stanley Hospital, a major tertiary hospital in Western Australia. All patients had newly diagnosed Burkitt Lymphoma, treated between January 1st 2016 and 3rd July 2020. Basic statistical data was generated using SPSS including Kaplan-Meir curves.

Results:
The median age was 45 with 79% of patients being male. 63% presented with Stage III/IV disease, 79% with elevated LDH and 68 % with extra-nodal disease. The most commonly prescribed regime was Dose-adjusted (DA)-R-EPOCH (53%). Both 1 and 2 year survival rates were 78%. 3 out of 5 rural patients had a time-to-treatment greater than 2 weeks, compared to 3 out of 14 metropolitan patients.

Conclusion: In comparison to the largest known retrospective analyses of Burkitt Lymphoma patients[1], baseline characteristics were similar but overall 2 year survival was higher in our single centre review. This may simply be a reflection of sample size but is potentially related to the higher use of DA-R-EPOCH at our centre (53% vs 30%). All deaths occurred within 1 year, consistent with the aggressive nature of the disease if unresponsive to initial therapy. Rural patients may experience a delay in treatment, highlighting a role for reviewing barriers to early delivery of care.

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H063

Epidemiology and therapeutic trends of T- and NK-cell lymphomas in an Australian cohort: an analysis of the Lymphoma and Related Diseases Registry (LaRDR)

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Aim: Distinct differences in T and NK-cell lymphoma epidemiology are recognized between Europe/Northern America and Asia[1,2], but Australian literature is lacking. This study aimed (1) to identify the frequencies of T/NK-cell lymphomas and (2) to determine treatment approaches to both newly-diagnosed and relapsed/refractory patients in an Australian context.

Method: Patients with mature T- or NK-cell neoplasia by the WHO 2016 classification were identified from LaRDR, which prospectively enrols patients over the age of 18 at participating centres. Baseline characteristics, frontline and salvage therapies, and survival outcomes were compared to published international data.

Results: From July 2016 to March 2021**,** 203 patients were identified across 23 sites. Median patient age was 62 years (range 19-93), 61% were male, and 67% presented with stage III/IV disease. Most common lymphoma types were (Table 1): peripheral T cell lymphoma NOS (PTCL-NOS, 57 patients, 28%), ALK-negative anaplastic large cell lymphoma (ALK- ALCL, 43 patients, 21%), angioimmunoblastic T-cell lymphoma (AITL, 31 patients, 15%), and extranodal NK/T cell lymphoma (ENKTL, 22 patients, 11%). With median follow-up of 9.2 months, estimated median overall survival was not reached; median progression-free survival from first treatment was 15.6 months (95% CI 9.8-26.0). Frontline CHOP/CHOEP-like regimens were given in 88% of patients with PTCL-NOS, ALCL and AITL, and overall response (CR/PR) to frontline treatment was 71%. For ENKTL, combination chemoradiotherapy was the favoured frontline treatment (63%). No preferred salvage therapies were noted in either subtype. Autologous and allogeneic transplants were performed in 26 and 6 patients respectively, with 16 autologous and 2 allogeneic transplants performed frontline in CR1/PR1.

Conclusion: This Registry study of Australian T- and NK-cell lymphoma patients demonstrates epidemiology similar to Europe/North America, with PTCL-NOS being the most prevalent lymphoma type, followed by ALK-ALCL, AITL, and ENKTL. Although a majority of patients received CHOP/CHOEP-like treatment first-line, heterogeneity in salvage and transplantation strategies was noted.

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Table 1: Frequencies of T cell lymphomas, *N* = 203

WHO 2016 classification	N (%)
Peripheral T cell lymphoma, NOS	57 (28%)
Anaplastic large cell lymphoma, ALK negative	43 (21%)
Anaplastic large cell lymphoma, ALK positive	9 (4.4%)
Angioimmunoblastic T-cell lymphoma	31 (15%)
Extranodal NK/T cell lymphoma, nasal type	22 (11%)
Adult T-cell leukaemia/lymphoma	6 (2.9%)
Subcutaneous panniculitis-like T cell lymphoma	6 (2.9%)
Enteropathy-associated T-cell lymphoma	5 (2.5%)
Hepatosplenic T cell lymphoma	5 (2.5%)
Other/unspecified	19 (9.4%)

Ibrutinib in relapsed/refractory mantle cell lymphoma (RR-MCL): interim analysis of outcomes on a Named Patient Program from the Lymphoma and Related Diseases Registry

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Aim: Chemotherapy-based salvage for RR-MCL is associated with significant morbidity and limited durability. Bruton's tyrosine kinase inhibitors (BTKi) have an established role in management of patients with RR disease. We describe an historical cohort of Australian patients with RR-MCL treated with ibrutinib on a 'Named Patient Program' (NPP).

Method: Patients treated with ibrutinib between 1st December 2014 and 30th November 2018 were identified from 13 participating centres via a centralised, de-identified database, the Lymphoma And Related Diseases Registry (LaRDR). Baseline characteristics and outcomes were compared to published trial data.

Results: 32 patients treated with ibrutinib for RR-MCL were identified, of an estimated 81 patients LaRDR-registered patients and a total of 300 patients with access to NPP supply. 76% were male, median age at diagnosis was 71.6 years, and all had ECOG □2. Median prior lines of therapy was 1 (range 1-3) and median time from MCL diagnosis to ibrutinib treatment was 1.9 years (range 0.2-8.5). Follow-up data was complete in 21 patients at time of writing, in whom 7 (33%) achieved a partial or complete response. With median follow-up of 1 year from commencement of ibrutinib therapy, Kaplan-Meier estimated median progression-free survival (PFS) and overall survival (OS) were 9.9 months (95% CI 2.1-12.9) and 14.0 months (95% CI 5.3-29.6) respectively.

Conclusion: Compared with data from international trials [1,2], this cohort of Australian RR-MCL patients had similar prior lines of treatment and performance status, but older age. PFS and OS were lower than outcomes reported in trials, reasons for which merit exploration with further follow-up. An updated analysis will be presented at the 2021 Blood meeting.
Study funded by Janssen.

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H065

Transformation of Follicular Lymphoma to lymphocyte deplete classical Hodgkin Lymphoma – a case report

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Introduction: Follicular lymphoma (FL) is an indolent B-cell lymphoma characterised by the pathognomic t(14;18) and IGHG1-BCL2 fusion gene with resulting overexpression of BCL2, an anti-apoptotic protein[1,2]. 3% of FL patients per year will undergo histologic transformation to an aggressive lymphoma, most commonly DLBCL[3,4]. Rare cases of transformation to Hodgkin Lymphoma have been described[5], however transformation to lymphocyte deplete HL (LDHL) has not previously been published. LDHL accounts for less than 1% of cHL in Western countries[6,7], often presents with advanced disease and carries a poor prognosis[8]. We report the first published case of LDHL transformed from underlying FL.

Case: A 39 yo woman presented with 2 months' fatigue, fevers, sweats and 14kg weight loss. Whole body CT/PET scan revealed a dominant 10.5cm infra-renal nodal mass (SUV max 19), widespread lymphadenopathy above and below the diaphragm (SUV max 14) and involvement of spleen and tonsil. Excisional biopsies of two cervical lymph nodes revealed dual pathology. Lymph node 1 was effaced by sheets of large atypical lymphoid cells, including Reed-Sternberg (RS) like cells (CD15+/30+/EBER-ISH neg), with sparse background small lymphocytes and eosinophils, consistent with LDHL. Lymph node 2 had a markedly different histologic appearance with an atypical follicular proliferation (CD20+/10+/BCL6+) and heavy interfollicular B cell infiltrate (CD20+, BCL2+) consistent with Grade 1 FL. FISH confirmed a BCL2 rearrangement in both the small B cells and RS-like large cells, suggesting a clonal relationship between both tumours. Bone marrow biopsy demonstrated heavy marrow infiltration by HL, confirming Stage IV_{BES} transformed Hodgkin lymphoma with a Hasenclever-IPI score 4 indicating high risk disease. She has commenced treatment with Rituximab and escalated BEACOPP.
Conclusion: This case documents the rare transformation from FL to LDHL, the least common variant of cHL. We will present further literature review, histology and clinical update at the conference.

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H066

Assessment of the clinical utility of next generation sequencing based evaluation of nodal peripheral T-cell lymphoma

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Aim: Providing accurate diagnoses of nodal peripheral T cell lymphoma (nPTCL) is a recognised challenge for haematologists/pathologists with a potential for incorrect diagnosis when relying on histopathological features alone. We sought to evaluate the clinical utility and role of NGS-based multi-gene panel assessment in the diagnostic workup of nPTCL.
Method: Cases referred to PMCC for comprehensive genomic evaluation as part of the diagnostic workup for suspected nPTCL were identified through the PMCC NGS database. NGS was performed using a custom Agilent SureSelect panel (PanHaem) targeting approximately 300 genes recurrently mutated in haematological malignancy as well as T-cell receptor (IGH/TCR) loci. Molecular results were correlated with the indication for testing, initial histological diagnosis and central pathology review. A diagnostic confidence score was assigned prior to and after molecular testing (uncertain, provisional, definitive) using pre-defined criteria.
Results: 69 consecutive cases were evaluated. 48/69 (70%) cases had variants detected by NGS. The most frequently mutated gene was *TET2*, seen in 37/69 (54%) cases. The most common molecular profile in the cohort was that of T follicular helper (TFH) phenotype (mutations in *TET2, DNMT3A, RHOA, IDH2* Arg172). The spectrum of mutations in patients with PTCL-NOS was heterogeneous and included *TET2, DNMT3A, JAK3, PLCG1, PLCG2, DDX3X, STAT3* and *TP53*. Comprehensive genomic testing improved the diagnostic confidence or changed diagnostic category in 30/69 (43%) cases over conventional classification using histology alone. The addition of NGS testing to histologic diagnosis alone resulted in a 48% reduction in the number of cases with an uncertain or provisional diagnosis (46/69 to 24/69) and an 83% increase in the number of cases with a definitive diagnosis (23/69 to 42/69).
Conclusion: Comprehensive genomic evaluation using targeted panel NGS is a clinically valuable tool for improving diagnostic certainty in the assessment of nPTCL, particularly in cases where the possibility of a TFH-derived subtype is being considered.

H067

Pirtobrutinib (LOXO-305), a next generation highly selective non-covalent Bruton's Tyrosine Kinase inhibitor in previously treated mantle cell lymphoma and other non-Hodgkin lymphomas: Phase 1/2 BRUIN study results

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Aim: To evaluate the safety and efficacy of pirtobrutinib in previously treated patients (pts) with MCL and other NHLs.
Method: The BRUIN trial is a multicenter phase 1/2 trial (NCT03740529) evaluating oral pirtobrutinib in pretreated pts with advanced B-cell malignancies. The primary endpoint was MTD/RP2D identification. This work was previously presented at ASH 2020.
Results: As of 27 September 2020, 323 pts with B-cell malignancies (170 CLL/SLL, 61 MCL, 26 WM, and 66 other B-cell lymphomas) were treated on 7 dose levels (25-300mg QD). Pirtobrutinib demonstrated high oral exposures, with doses ≥100mg QD exceeding the BTK IC90 for the entirety of the dosing interval. No DLTs occurred. The only TEAEs regardless of attribution or grade in ≥10% of pts (n=323) were fatigue (20%), diarrhea (17%) and contusion (13%). A RP2D of 200mg QD was selected. At the efficacy cutoff date, 35 (57%) MCL pts, 18 (69%) WM pts and 34 (52%) other NHL pts remained on therapy. Among the 52 efficacy evaluable prior BTKi treated MCL pts, the ORR was 52%. Among the 19 efficacy-evaluable pts with WM, the ORR was 68%. For the 55 efficacy-evaluable other NHL pts, ORR was 24% (DLBCL), 50% (FL), 22% (MZL), and 75% (Richter's transformation).
Conclusion: Pirtobrutinib demonstrated promising efficacy in MCL and other NHL pts, was well tolerated and exhibited a wide therapeutic index.
This research was supported by Loxo Oncology at Lilly. The sponsor played a role in the analysis and interpretation of data in collaboration with all authors.

H068

Frailty Assessment in Elderly patients with Diffuse Large B cell lymphoma (DLBCL): Exploring the use Clinical Frailty Score (CFS) and its impact on predicting mortality and morbidity.

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Aim: Delivery of optimal care to older patients with haematological cancers can be challenging due to heterogeneity in their functional reserves. There is a paucity of data using frailty indices to predict outcomes. We explore the utility of Clinical Frailty Score as a frailty assessment tool in predicting toxicities and survival.

Method: We performed a retrospective, single centre study on all patients aged > 60 with DLBCL managed at Northern Health between 2013-2020. Clinical frailty score was retrospectively assigned by investigators after reviewing clinical documentation. Descriptive statistics and univariate analyses were performed using T Test and Chi Square testing. All analyses were performed using Microsoft Excel (Microsoft corp., WA).

Results: 55 patients with a mean age of 73.4 years were evaluated, with 40% defined as frail on CFS (Score >3) vs 29% on Eastern Cooperative Oncology Group (ECOG) (Score ≥2) at diagnosis. 68% (38/56) had at least one unplanned admission, with 28.5% (16/56) requiring upfront chemotherapy dose reduction. Two-year overall survival is 76% with 27.7 months median follow up.
Both CFS > 3 and ECOG ≥ 2 highlighted a cohort of patients with higher age (mean = 78.5) and International Prognostic Index (Median = 4). There are strong associations between both frailty indices with prolonged hospital admissions (67% & 75%; p<0.01) and upfront dose reductions (55% & 64%; p< 0.01). 2 year survival is significantly lower: 59% for CFS >3 group and 50% for ECOG≥ 2 group.

	CFS >3 (n =22)	CFS ≤3 (n =23)	
Mean Age (years)	78	71	p < 0.01
Median R-IPI	4	3	p = 0.04
R-MiniCHOP	13 (59%)	4 (12%)	p < 0.01
Upfront Dose Reduction	11 (50%)	5 (15%)	p < 0.01
Admissions > 7 days	14 (67%)	6 (18%)	p <0.01
Admissions with geriatric syndrome	9 (41%)	3 (9%)	p =0.01
2 year overall survival	13 (59%)	29 (88%)	p =0.03

Conclusion: This study supports Clinical Frailty Score as a useful frailty screening tool. More frail patients appear to be captured using CFS than ECOG screening, though their ability to predict mortality and major morbidities are similar. Prospective interventional studies incorporating Comprehensive Geriatric Assessment and supportive care referral may shed light into the functional needs of these frail patients who remain in the community during their treatment.

H069

Glofitamab step-up dosing (SUD): updated efficacy data show high complete metabolic response (CMR) rates in heavily pretreated relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) patients

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Aim: We present updated glofitamab monotherapy SUD with obinutuzumab pretreatment (Gpt) efficacy data from the ongoing, Phase I dose-escalation and expansion study (NP30179/NCT03075696) in heavily pretreated R/R NHL patients.

Method: Gpt (1000mg) was given 7 days pre-glofitamab initial dose. Intravenous glofitamab SUD was given on Day (D) 1 and 8 of Cycle (C) 1 and then at the target dose from C2D1 (2.5/10/16mg or 2.5/10/30mg); treatment continued for up to 12 cycles, every 21 days. Response rates were based on the Lugano criteria1.

Results: Fifty-two patients received glofitamab SUD (2.5/10/16mg, n=17; 2.5/10/30mg, n=35). 53.8% patients had aggressive NHL (aNHL) and 46.2% had indolent NHL (iNHL). 76.9% and 73.1% patients were refractory to their most recent and any prior CD20 therapy, respectively. An updated efficacy analysis was conducted after a median follow-up of 6.3 months. For 28 aNHL patients, the best overall response (OR) and CMR rates were 64.3% and 57.1%, respectively; a trend of improved CMR of 71.4% was observed with increased target dose at 2.5/10/30mg (n=14). 4/5 mantle cell lymphoma patients had CMR (2.5/10/16mg, n=2; 2.5/10/30mg, n=2). For aNHL, 13/16 CMRs are ongoing, with 8 lasting >3 months. For iNHL, OR and CMR rates were 79.2% and 70.8%, respectively; 14/17 CMRs are ongoing, with 10 lasting >3 months. Common adverse events were CRS (63.5%), neutropenia (38.5%), and pyrexia (32.7%). Most CRS occurred in C1: 24/50 patients had CRS after 2.5mg; 20/49 after 10mg; 2/16 and 8/32 after 16 and 30mg (C2D1), respectively. Grade 1 and 2 CRS was reported in 34.6% and 23% patients, respectively; 5.8% had Grade 3; none had Grade 4/52.

Conclusion: Updated data for glofitamab monotherapy SUD show higher preliminary response rates than previously reported in heavily pretreated R/R NHL patients. CRS was mostly manageable, of low grade, and confined to C1.

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H070

Excellent outcomes for allogeneic bone marrow transplantation in Sezary syndrome: results of Australian multicentre analysis.

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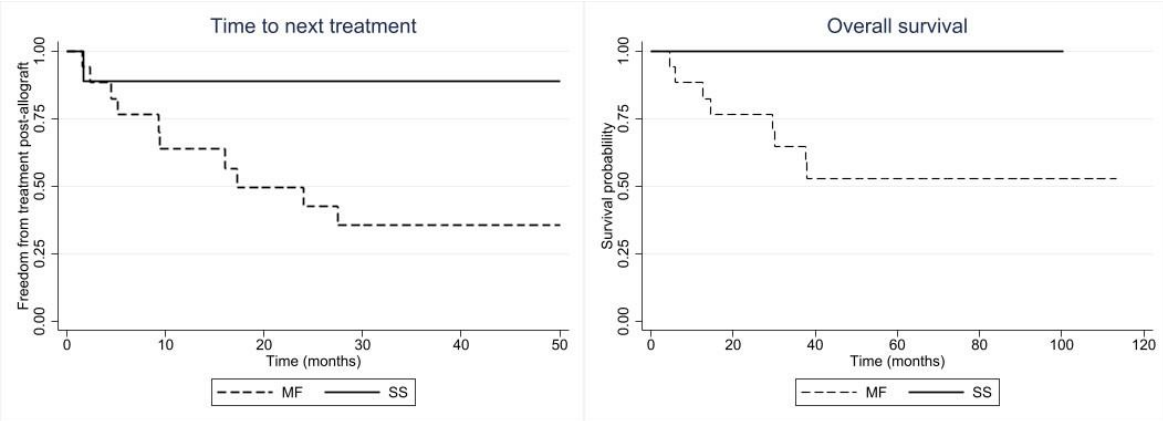
Aim: Sezary syndrome (SS) and mycosis fungoides (MF) are often analysed together when investigating outcomes of allogeneic bone marrow transplantation (alloBMT) for cutaneous T cell lymphomas (CTCL). However, these are distinct clinicopathologic entities that may respond differently to alloBMT. We investigated alloBMT outcomes in SS and MF patients.

Method: A multicentre retrospective cohort study was performed at four transplant centres across Melbourne, Brisbane, Sydney and Adelaide. Patients with SS or MF undergoing allograft from 01/01/2008–31/12/2019 were included and outcome data compared between groups. Time-to-next-systemic treatment (TTNT) was used as a surrogate measure of disease relapse. Statistical analysis was performed using Stata/IC v16.1, using Fisher's exact for categorical data, Wilcoxon rank-sum for non-parametric data, Kaplan-Meier survival analysis, and multivariate logistic regression for independent outcome predictors.

Results: A total of 26 patients underwent alloBMT during the study period (17 MF, 9 SS). Matched related donors were more common in the SS group (66.7% vs 17.7%, p=0.03); there was no significant difference between groups regarding age, sex, interval from diagnosis to transplant, prior lines of therapy, disease stage and remission status pre-transplant, conditioning intensity, or use of T-cell depletion with transplantation. Median follow-up was 5-years. Compared with MF, SS patients had lower need for systemic treatment for disease relapse (11.1% vs 70.6%, p=0.01), longer median TTNT (not reached vs 17.2 months, p=0.009), and lower mortality rates (0% vs 47.1%, p=0.02) (figure 1). Mortality in MF patients was distributed equally between relapse and non-relapse mortality. On multivariate analysis, disease subtype independently predicted need for systemic treatment for relapse, with SS conferring protective effect (OR 0.02, 95%CI 0.001–0.69, p=0.03). There were no differences in engraftment or GVHD between groups.

Figure 1. TTNT and OS curves in CTCL patients following allo-BMT.



Conclusion: SS and MF have significantly different relapse and survival outcomes following alloBMT. Excellent outcomes in SS suggest that alloBMT should be considered early in management decision making.

Exploratory analysis of the randomized phase 3 KEYNOTE-204 study to evaluate pembrolizumab monotherapy versus brentuximab vedotin in patients with relapsed/refractory classical Hodgkin lymphoma (R/R cHL) by prior lines of therapy

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Aim: The purpose of this post hoc exploratory analysis of KEYNOTE-204 (NCT02684292) was to evaluate pembrolizumab compared with brentuximab vedotin (BV) by number of prior lines of therapy.

Method: Adult patients with R/R cHL who had measurable disease and ECOG PS 0 or 1 and who were ineligible for or experienced relapse after autologous stem cell transplant (ASCT) were eligible for this trial. Patients were randomly assigned 1:1 to pembrolizumab 200 mg IV every 3 weeks (Q3W) or BV 1.8 mg/kg IV Q3W. Primary end points were PFS by blinded independent central review per International Working Group criteria, including clinical and imaging data after ASCT, and OS. Additional end points included ORR and safety.

Results: Of 304 randomly assigned patients, 55 (pembrolizumab, 27; BV, 28) received 1 prior therapy and 249 (pembrolizumab, 124; BV, 125) received ≥2 prior therapies. For the primary PFS analysis, median PFS was 16.4 months for pembrolizumab and 8.4 months for BV (HR, 0.70; 95% CI, 0.31-1.59) and 12.6 months for pembrolizumab and 8.2 months for BV (HR, 0.66; 95% CI, 0.47-0.92) for patients who received 1 and ≥2 prior therapies, respectively. ORR was 66.7% for pembrolizumab and 53.6% for BV in the 1 prior therapy group and 65.3% for pembrolizumab and 54.4% for BV in the ≥2 prior therapies group. 3.7% and 29.6% of patients receiving pembrolizumab and BV, respectively, experienced grade 3-5 treatment-related adverse events (TRAEs) after 1 prior therapy, whereas 23.1% and 24.0% of patients receiving pembrolizumab and BV, respectively, experienced grade 3-5 TRAEs after ≥2 prior therapies.

Conclusion: Compared with BV, pembrolizumab monotherapy resulted in improved PFS and ORR in patients with R/R cHL regardless of number of prior therapies. These data suggest that pembrolizumab monotherapy is a promising option as 2L+ therapy for patients with R/R cHL ineligible for ASCT.

H072

Feasibility of longitudinal assessment of cancer-related cognitive impairment in people newly diagnosed aggressive lymphoma.

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Aim: Cancer-related cognitive impairment (CRCI) is a recognised adverse consequence of cancer and its treatment occurring in up to 75% of patients. For some cognitive impairment may be transient, but for a subgroup these symptoms can be long-standing and have a major impact on quality of life. The aim of this prospective longitudinal study was to assess the feasibility of collecting longitudinal data on cognition using subjective and objective assessment of people with newly diagnosed, aggressive lymphoma undergoing standard therapy with curative intent.

Methods: Eligible participants completed repeated measures of cognition including self-report, neuropsychological assessment, blood cell–based inflammatory markers, and brain imaging including PET/CT and MRI at three pre-specified time-points, Time 1 (T1) – pre-treatment (treatment naïve), Time 2 (T2) – mid-treatment, and Time 3 (T3) – six to eight weeks post-completion of treatment.

Results: Of 33 eligible participants, 30 (91%, 95% CI: 76%, 97%) were recruited over 10 months. The recruitment rate was 3.0 patients/month (95% CI: 2.0, 4.3 patients/month). Reasons for declining included feeling overwhelmed and the rapid start of treatment. Mean age was 57 years (SD=17 years) and 16/30 (53%) were male. Most patients (20/30, 67%) had diffuse large B cell lymphoma or Hodgkin lymphoma (4/30, 13%). The neuroimaging sub-study was optional, 11/30 participants (37%) were eligible to take part and all agreed. Retention and compliance with all assessments was very high at all time-points. Only two patients withdrew, both due to disease progression.

Conclusions: Our findings indicate it is feasible to complete a comprehensive assessment of cognitive outcomes in people with newly diagnosed aggressive lymphoma during their initial treatment. These results suggest longitudinal assessment of cognitive function in patients during treatment and recovery should be undertaken to inform interventions to reduce cognitive impairment and its impact in lymphoma populations.

H073

Clinical efficacy of mosunetuzumab in patients with multiply relapsed follicular lymphoma

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Aim: To present updated safety and efficacy clinical data from patients with R/R follicular lymphoma (FL) after at least two prior systemic therapies treated with mosunetuzumab from an ongoing open-label, multicenter, Phase I/Ib, dose-escalation and expansion study/NCT02500407.

Method: Patients received intravenous mosunetuzumab monotherapy as step-up doses in Cycle 1 on Day 1 and 8 and the target dose on Day 15. Mosunetuzumab was given on Day 1 of each subsequent 21-day cycle for 8 cycles in patients with a complete response (CR), and up to 17 cycles in those with a partial response (PR) or stable disease.

Results: 62 R/R FL patients (with at least two prior systemic therapies), received mosunetuzumab at dose levels between 0.4/1.0/2.8mg and 1/2/13.5mg (Cycle 1 Day 1/8/15 dose levels). 53% were refractory to both a prior anti-CD20 antibody and an alkylating agent, 48% had POD24, and 6% had received prior chimeric antigen receptor T-cell therapy.

Overall response rate (ORR) was 68%, with 50% patients achieving CR. Consistent CR rates were observed in high-risk patient populations. Median time on study was 14.4 months, 62% of all responders (including 74% that achieved CR) remained in remission at data cut-off. Median duration of response (DOR) was 20.4 months for all 42 responders. Median PFS was 11.8 months. AEs were reported in 97% patients, SAEs in 35% patients. The most frequent grade ≥3 AEs included hypophosphatemia (23%) and neutropenia (21%; 2% febrile neutropenia). 14 (23%) patients experienced reversible CRS, mostly of Grade 1 or 2, and only during Cycle 1. No CRS required tocilizumab, ICU or vasopressor. Neurologic AEs (NAEs) were observed in 28 patients; all were Grade 1 or 2.

Conclusion:
Fixed-duration mosunetuzumab monotherapy results in high response rates and durable disease control with a tolerable safety profile in R/R FL patients, including known high-risk subgroups.

H074

Salvage radiotherapy associates with durable response for a subset of patients with limited stage refractory diffuse large B-cell lymphoma

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Aim: One-third of patients with diffuse large B-cell lymphoma experience relapsed or refractory disease portending poor prognosis. The study was conducted to assess outcomes of patients treated with salvage radiotherapy for limited stage relapsed / refractory DLBCL (rrDLBCL) to determine its utility and inform future treatment algorithms.

Method: DLBCL cases (867 patients) at Monash Health, Melbourne, Australia, between 1996 - 2019 within the Haematology Database were analysed. Adult patients with rrDLBCL (including transformed indolent lymphoma) treated with salvage radiotherapy alone with curative intent were included in the study. Patients with inadequate clinical information or follow up data available or those in whom radiotherapy was administered as consolidation or clearly palliative intent were excluded.

Results: From 1996-2019, 18 patients were identified for inclusion in the study (12 refractory / 6 relapsed). 11/18 had biopsy-proven refractory disease, a further 3/18 had inconclusive biopsy with high suspicion of active disease on imaging and remaining patients were treated on basis of high clinical suspicion from PET imaging with sites not amenable to biopsy. Median radiotherapy dose was 42 Gy (10-50). After median follow up of 14 months (1-64), 11/18 patients progressed (Fig. 1) after a median of 2 months (0-13). 7/18 (39%) patients remain in ongoing remission without any progression events after median of 29 months (13-64). Of the primary refractory subset, 4/12 (33%) remain free from progression with median follow up of 32 months (13-64).

Conclusion: Salvage radiotherapy confers meaningful disease control for a subset of patients with limited stage rrDLBCL. Despite the small sample size and retrospective nature of the study, we conclude salvage radiotherapy should be considered a treatment option for patients ineligible for salvage chemotherapy in cases of single site rrDLBCL. These findings warrant further clinical investigation.

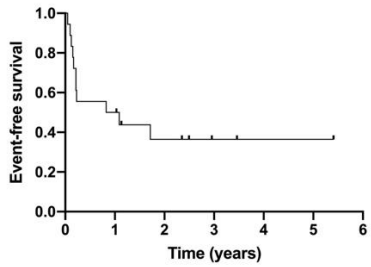

Fig 1. Event-free survival from radiotherapy commencemen

H075

Effect of Age on the Efficacy and Safety of Single Agent Oral Selinexor in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL): Post-Hoc Analysis from the SADAL Phase 2b Study

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Aim: Selinexor, a first-in-class selective inhibitor of nuclear export is FDA approved for RR DLBCL based on the SADAL study. Patients with RR DLBCL tend to be older (>65) with comorbidities, limiting use of aggressive therapies. A post-hoc analyses was performed to determine effects of age on efficacy and safety.

Method: SADAL is an open-label Phase 2b study of Selinexor (administered orally at 60 mg twice weekly until disease progression) in DLBCL patients with 2-5 lines of prior therapy. Outcomes were assessed in patients <65 vs. ≥65.

Results: 39% were <65 and 61% were ≥65. Subtype analysis: 43% GCB and 55% non-GCB in ≥65, and 54% GCB and 40% non-GCB in the <65.

Patients < 65 received numerically higher median doses (1360 and 770 mg [p=0.079]) and longer treatment duration (13.5 vs. 8.0 weeks [p=0.049]). No statistical difference in ORR in patients <65 vs. ≥65: 36.5% vs. 24.4% (p=0.189). CR rates were 17.3% and 11% (p=0.431), respectively. Median DORs and median PFS were similar (9.7 months vs. 9.2 months) and (3.6 and 2.3 months), respectively. OS was higher in <65: 13.7 vs. 7.8 months (p=0.037).
Treatment-related AE incidence was comparable: most common grade ≥3 AEs in <65 vs. ≥65 were thrombocytopenia (42.3% vs. 39.0%), nausea (3.8% vs. 7.3%), and fatigue (5.8% vs. 13.4%). Treatment-related serious AEs occurred in 11.5% of patients <65 (n=6) and 26.8% ≥65 (n=22), with general disorders and administration site conditions (n=12) and fatigue (n=6) as the largest contributors in the ≥65 group. Treatment discontinuations due to AEs were lower in the <65 vs. >65 (3.8% vs. 11.0%).

Conclusion: Similar clinical benefit in RR DLBCL patients ≥65 and <65 (comparable efficacy and safety). Younger patients had longer OS, likely due to comorbidities in older patients. Selinexor can induce durable responses in RR DLBCL patients with similar tolerability.

Selinexor Efficacy and Safety are Independent of Renal Function in Patients (pts) with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL): A Post-Hoc Analysis from the Pivotal Phase 2b SADAL Study

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Aim: Selinexor, an oral, first-in-class selective inhibitor of nuclear export is FDA approved for RR DLBCL based on the SADAL study. RR DLBCL pts tend to have comorbidities, including renal dysfunction. Selinexor is not metabolized by the kidneys. We aim to assess efficacy and safety of selinexor in pts with renal impairment.

Method: SADAL is an open-label Phase 2b study of selinexor in DLBCL pts with 2-5 lines of prior therapy. Outcomes were assessed according to baseline renal function in pts with reduced creatinine clearance (CrCl ≤60 mL/min) and normal renal function (CrCl >60 mL/min). A post-hoc analyses was performed to determine outcomes in pts stratified by baseline renal function.

Results: 28% of pts had reduced baseline CrCl (≤60 mL/min) while 72% had CrCl >60 mL/min. Median age in reduced CrCl group was 74 years (70% ≥70 years). Median age for normal CrCl group was 65 years (35% ≥70 years). ORR in pts with reduced CrCl (29.7%) vs. normal CrCl (28.9%) was similar. CR was 21.6% in pts with reduced and 10.3% in pts with normal CrCl. Median DOR in patients with reduced CrCl was 23.0 months vs. 9.2 months in pts with normal CrCl. Median PFS was 3.5 months vs. 2.3 months and OS was 7.8 months vs. 9.1 months in pts with reduced vs. normal CrCl. The most common grade ≥3 treatment-related AEs for pts with reduced vs. normal CrCl were thrombocytopenia (45.9% vs. 38.1%), nausea (5.4% vs. 6.2%), and fatigue (8.1% vs. 11.3%). There was no clinically significant increase in treatment-related serious AEs (21.6% vs. 20.6%) and AEs leading to discontinuation (10.8% vs. 7.2%) in pts with reduced vs. normal CrCl, respectively.

Conclusion: Selinexor demonstrated similar activity and tolerability in pts with RR DLBCL with reduced compared to normal renal function. No selinexor dose adjustments are required for renal dysfunction.

H077

Dural marginal zone lymphoma successfully treated with single agent rituximab

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Background: Dural marginal zone lymphoma is a rare CNS lymphoma that arises from the dura mater. Involvement of brain parenchyma is not seen and the disease is associated with a favourable prognosis. Due to the rarity of this condition, the most appropriate treatment strategy has not been elucidated. Combinations of surgical resection coupled with focal or whole brain radiotherapy, with or without systemic chemotherapy, are the preferred approaches. The utility of single agent rituximab, which is commonly employed for nodal and extranodal marginal zone lymphoma, has not been described for the treatment of dural marginal zone lymphoma.

Case: A 59 year old female presented with a several week history of headaches, left hemiparesis, slurred speech, and diplopia. She was initially misdiagnosed as an acute intracranial haemorrhage on MRI. She underwent stereotactic biopsy of a right dural mass demonstrating dural marginal zone lymphoma. PET-CT did not demonstrate any evidence of malignancy beyond the dural mass. It was deemed to be not amenable to resection or radiotherapy. She received four cycles of rituximab over four weeks, and made a complete clinical and radiological recovery. There is no evidence of progression almost two years after completion of therapy.

Conclusion: Given the complications associated with WBRT and high-dose methotrexate, including neurotoxicity, leukoencephalopathy, and cognitive impairment, this case highlights that single agent rituximab may obviate the need for chemotherapy and/or radiotherapy for dural marginal zone lymphoma.

H078

Subcutaneous (SC) mosunetuzumab demonstrated promising safety and efficacy in relapsed or refractory b-cell lymphoma (R/R B-NHL) in dose escalation cohorts

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Aim: We aim to present safety profile and clinical efficacy of alternative SC administration of monsunetuzumab, to minimize the risk of cytokine release syndrome (CRS) in patients with R/R B-NHL.

Method: R/R B-NHL patients from the Phase I/Ib, open-label, multicenter dose-escalation and expansion study GO29781 received single-agent mosunetuzumab SC on Day 1 of each 21-day Cycle (Q3W), for 8 cycles in patients with complete response (CR) and up to 17 cycles in patients with partial response or stable disease; dose escalated from 1.6–20 mg.

Results: 23 patients received mosunetuzumab SC, 57% were refractory to prior therapies and 70% to prior anti-CD20 therapy. MTD was not reached, one dose-limiting toxicity at dose 1.6mg (Grade 4 neutropenia; resolved). 96% patients experienced ≥1 AE, common AEs related to treatment were CRS (35%), headache (22%) and injection site reaction (22%), and no AEs led to treatment discontinuation. All CRS events occurred during Cycle 1 and were Grade ≤2[1]. 15% of Q3W IV fixed-dose patients experienced Grade 2 CRS at doses 0.05–2.8mg, no Grade 2 CRS occurred in SC cohort at doses <13.5mg. Overall response rates and CR rates were 86% and 29% in indolent NHL patients, 60% and 20% in aggressive NHL patients, respectively. All but one CR SC patient remained in remission at cut-off date (median time on study 6.9 months). Mosunetuzumab SC pharmacokinetic profile demonstrated a slow absorption rate and ~70% reduction of Cmax versus IV, consistent with reduced CRS, lower peak IL-6 levels, and delayed onset with SC dosing.

Conclusion: Mosunetuzumab SC demonstrated a promising safety and efficacy profile, and pharmacokinetics in R/R B-NHL patients. CRS events seen in Cycle 1 were mild and reversible, and less Grade 2 CRS at 7-fold higher dosage than IV. These results support continued dose escalation and optimization of mosunetuzumab SC in R/R B-NHL.

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H079

Neurolymphomatosis (NL): A rare neurological complication of lymphoma

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Aim: Neurolymphomatosis (NL) is a rare neurologic complication of lymphoma and poses a diagnostic challenge because of its rarity and variability in presenting clinical features. We present a case of NL diagnosed by nerve biopsy in a patient with mantle cell lymphoma (MCL)

Method: Clinical, laboratory, and therapeutic data from a case report is described. The literature was examined for previously reported cases of neurolymphomatosis.

Case:A 65 y.o male with previously untreated stage IV MCL, stable under observation with no indications for treatment, presented with 3 days of bilateral lower limb weakness, preceded by 2 weeks of upper respiratory tract infection symptoms. Initial neurological examination revealed bilateral lower motor neuron signs in the lower limbs. Nerve conduction studies (NCS) suggested a diagnosis of Guillain-Barre syndrome (GBS).

A 5 day course of intravenous immunoglobulin (IVIg) resulted in an initial improvement in his neurology. He subsequently developed a decline in his neurological symptoms and signs, with progressive demyelination on repeat NCS. A second course of IVIg was trialled with no improvement. Repeat imaging revealed progressive lymphadenopathy and splenomegaly.

A diagnostic sural nerve biopsy revealed features suggestive of NL with lymphocytic infiltration within the intersitium. A single cycle of bendamustine-rituximab was commenced, with a plateau in response, followed by ibrutinib with marked improvement in his neurological symptoms.

Results: To our knowledge, there have been two previously reported cases of neurolymphomatosis in MCL.

Conclusion: Mantle cell lymphoma accounts for 5-10% of Non-Hodgkin Lymphoma (NHL). The reported frequency of NL in cases of NHL ranges from 0.2% - 0.5%. There are two cases previously reported on NL in MCL. Nerve biopsy is the gold standard for diagnosis. In patients with NHL with unexplained, progressive neurology, a nerve biopsy should be considered for the diagnosis of NL.

H080

Treatment of diffuse large B-cell lymphoma and high-grade B-cell lymphoma in a regional centre

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Aim: To evaluate first-line treatment practices and outcomes for diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) in a regional tertiary teaching institute.

Method: Retrospective analysis of newly diagnosed DLBCL and HGBL patients treated at Sunshine Coast University Hospital from 2017-2019. Data was collated from electronic medical records.

Results: There were 46 patients, 18 female, median age 73 years. 33 patients had DLBCL, 6 HGBL-double hit (HGBL-DH), 7 HGBL-NOS, including 8 with transformed lymphoma. The median follow up time was 25 months.

9/16 patients ≥75 years received R-miniCHOP achieving 56% complete response (CR), with remaining 7/16 receiving RCHOP achieving 71% CR. 4/6 patients with HGBL-DH received R-EPOCH and 2/6 RCHOP, achieving 67% CR overall. 1/3 patient with secondary CNS involvement received R-MPV with treatment related mortality, whereas 2/3 received RCHOP with CNS directed methotrexate to CR. The remaining patients with DLBCL and HGBL received RCHOP with 74% achieving a CR.

CNS prophylaxis was administered to 16 patients. This included 5/6 patients with HGBL-DH, 8/16 high-risk CNS-IPI, 1/1 testicular involvement and 0/1 kidney/adrenal involvement. Two other patients received CNS prophylaxis, one with isolated maxillary sinus DLBCL and another double expressor DLBCL.

Overall, 18-month PFS was 70% and 18-month OS 70%. 14 patients died, including 8/8 patients with refractory disease (3/8 had second line therapy with no response), 1/1 relapsed disease, 1/1 treatment related, with remainder not directly related to lymphoma.

Conclusion: Patients with DLBCL and HGBL are diverse with regards to their disease risk profiles and response to treatment. This study outlines a poor prognosis in elderly patients who cannot tolerate standard dose chemotherapy and those with refractory disease, highlighting the need for improved treatments in these patient groups. Outcomes were comparable to other published studies.[1-3]

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H081

Genomic profiling of CD20 negative Diffuse large B cell lymphoma identifies targetable mutations: A case report

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Diffuse large B cell lymphoma (DLBCL) is a clinically and genetically heterogeneous non-Hodgkin lymphoma that usually expresses B-cell lineage antigens including CD20.[1] CD20 negative (CD20-) DLBCL is rare, and survival is reported to be worse than DLBCL-NOS (not otherwise specified) because of lack of efficacy of CD20 monoclonal antibodies.[2] New treatment targets are required to improve outcomes.

We report the first case of genomic profiling in CD20- DLBCL. We extracted genomic DNA from fresh frozen diagnostic tissue from a 90-year-old patient and performed next generation sequencing (NGS) targeting genes involved in lymphomagenesis.

Following mutated genes were identified in our patient: TANK and TNFRSF11a/RANK, EZH2, HIST1H1C, HIST1H1E, KMT2B, PRDM2, NOTCH2, ATM, BCOR, CIITA, SPEN, TCF3, and TYK2 genes, DTX1 ubiquitin ligase (three individual mutations located in WWE1 domain), ADAMTS5, SYNE1, ZFHX4, XPC, FCGR3A, and BRAF-V600E. Some of these are previously reported in DLBCL while others have been associated with lymphoproliferative disorders in general.

Mutations of prognostic relevance include NOTCH2, CIITA, ATM, KMT2B/MLL2, NF-κB pathway and DTX1 ubiquitin ligase mutations (WWE1 domain).

Targetable mutations including NOTCH, EZH2, TYK2 and BRAF-V600E were identified which may offer novel therapeutic options. γ-secretase inhibitor targeting NOTCH signalling for high risk CLL, oral EZH2 inhibitor Tazemetostat for relapsed or refractory FL, TYK2 inhibitor with activity against ALCL in a preclinical model and Vemurafenib targeting BRAF-V600E in Hairy cell leukaemia are examples of drugs that are either already being utilised in clinical practice or are under further investigation.

This is the first report on the mutational profile of CD20- DLBCL which has identified a number of targetable mutations that may provide alternative treatment options. Given the rarity of this subtype of lymphoma, international collaboration to genotype larger cohorts and identify recurrent mutations is required.

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H082

Plasma cells arise from differentiation of clonal lymphocytes and secrete IgM in Waldenström Macroglobulinaemia

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Background: Waldenström Macroglobulinaemia (WM) is an indolent non-Hodgkin lymphoma characterised by bone marrow infiltration with a malignant infiltrate of predominantly lymphoplasmacytic cells (LPCs) with a smaller population of plasma cells (PCs), and hypersecretion of IgM paraprotein.

Aim: We aimed to characterise the immunophenotype, molecular genetics and secretory function of PCs in two WM cell lines (MWCL-1 and BCWM.1), and a representative number of clinical patient samples.

Method: Using FACS, we identified LPCs as CD45bright/CD38dim/CD138-/CD19+/CD20+ cells and PCs as CD45dim/CD38+/CD138+ cells from both cell lines. Standard PCR and Sanger sequencing were used to assess MYD88 (using MYD88 L265P specific primers) and immunoglobulin heavy chain (IgHV) status (using Biomed2 specific primers for FR3).

Finally, to determine which population was predominantly responsible for IgM hypersecretion, isolated LPCs and PCs from both cell lines were cultured and the culture media was analysed by ELISA for IgM secretion at 72 hours.

Results: Using a conservative sorting strategy, we analysed both cell lines and demonstrated heterozygous MYD88-L265P mutation in both LPC and PC populations. We also observed the expression of the same auto-reactive IgHV sequences in both LPCs and PCs from MWCL-1 (VH3-15*01) and BCWM.1 (VH3-23*01), suggesting similar clonal origin and role for auto-antigens in WM cell survival.

Cell culture studies showed that PCs alone were primarily responsible for IgM production (8.7-9.3x10^3 ng/ml) despite relative lack of proliferation in MWCL-1 while those isolated from BCWM.1 produced 2.5-2.8x10^3 ng/ml of IgM. LPCs from both cell lines gave rise to the more differentiated PCs (7.5 – 9% PCs in MWCL-1 and 1.2-1.4% PCs in BCWM.1), and secreted smaller amounts of IgM than PCs (3.5-5.0x10^3 ng/ml in MWCL-1 and 0.3-0.7x10^3 ng/ml in BCWM.1).

Conclusion: Our analysis provides evidence to support the commonly held hypothesis that malignant PCs arise from the clonal LPC population, and are primarily responsible for IgM secretion in WM.

H083

A multicentre, parallel arm, open-label trial of frontline R-CHOP/Polatuzumab vedotin-RCHP and glofitamab in younger patients with higher risk diffuse large B cell lymphoma (DLBCL) (COALITION) – Trial in Progress

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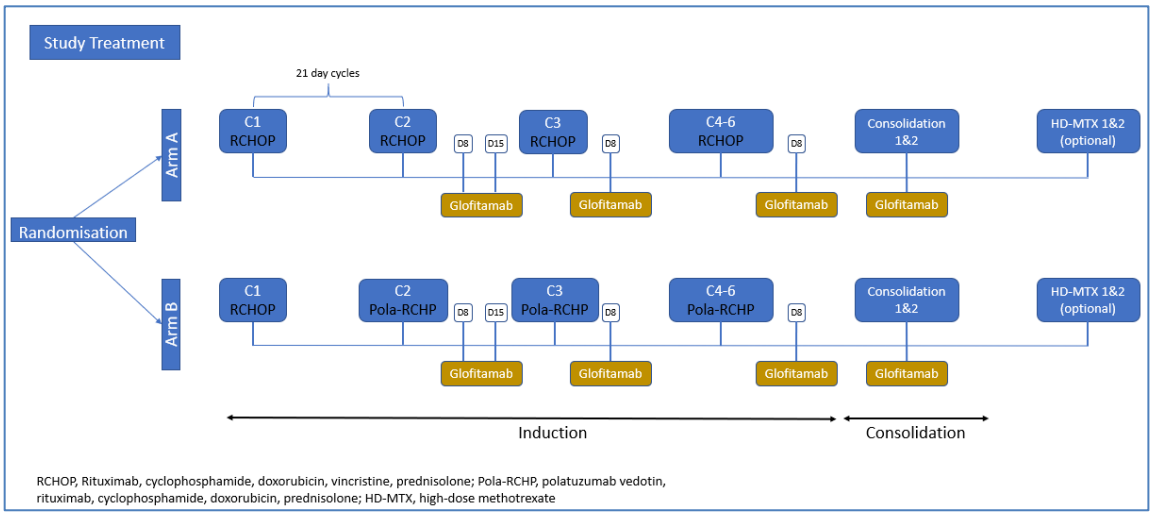
Aim: While the majority of patients with DLBCL and many with high grade B-cell lymphoma with double hit (HGBL-DH) are cured with 1L R-CHOP, in a significant proportion their disease will be refractory or relapse, particularly among those with high-risk features as defined by the IPI. Glofitamab is a novel full-length bispecific antibody with a unique 2:1 configuration (two CD20 binding domains and one CD3 binding domain). In combination with a single pre-dose of obinutuzumab, glofitamab has demonstrated >50% complete remission at the RP2D in a phase 1 trial (Hutchings, JCO 2021). The key toxicity is cytokine release syndrome. Pre-clinical studies suggest that glofitamab's activity is retained in the presence of cytotoxic therapies and CD20 antibody. Polatuzumab vedotin (pola) is an antibody-drug conjugate approved for R/R DLBCL in combination with BR, and in evaluation for the front-line treatment of DLBCL with RCHP.

The safety and preliminary efficacy of R-CHOP-glofitamab, or pola-RCHP-glofitamab as a front-line treatment for high risk DLBCL is being evaluated.

Method: This is a parallel-arm phase Ib/II trial. Treatment consists of an initial cycle of R-CHOP, followed by 5 cycles of combination treatment and 2 cycles of consolidation glofitamab monotherapy. Key inclusion criteria are: age 18-65 years, a diagnosis of DLBCL or HBGL, IPI ≥3 or NCCN-IPI ≥4, treatment naïve or after 1 cycle of R-CHOP, ECOG 0-3. The primary endpoint is the safety of the combination and secondary endpoints include complete response rates at interim and end of treatment FDG-PET assessments by Lugano criteria. Correlative studies are planned.

Approximately 40 patients will be treated in each arm across 10-12 Australian sites. It is anticipated the trial will open Q3 2021, and recruit for approximately 2 years. Interested sites should contact the PI.



H084

Tisagenlecleucel CAR T-cell detection and quantification by ddPCR in patients treated for DLBCL and B-ALL.

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Aim: Tisagenlecleucel is a CD19 CAR-T approved for use in DLBCL and paediatric/adolescent B-ALL. Despite a clinical need, assays to detect and quantify CAR-T are not routinely available. We report data on the quantification of tisagenlecleucel in peripheral blood using digital droplet PCR (ddPCR) in a cohort of patients with ALL and DLBCL.

Method: Patients underwent collection at early (day 5-12), intermediate (day 26-32) or late (day≥100) timepoints. Quantification was performed using duplex ddPCR combining assays for the CAR sequence and a reference gene and calculated as the number of CAR copies per µg of genomic DNA. The same assay was used to quantify CAR in cell free DNA (cfDNA) in a subset.

Results: Tisagenlecleucel CAR was detected in 26/27 patients (5 ALL, 22 DLBCL) at one or more timepoints. 10 patients had sequential samples. Median CAR copies at early, intermediate, and late timepoints were 2506 (range 0 – 113280 copies/µg), 612 (range 80 – 9744 copies/µg) and 121 (range 10 – 412 copies/µg). CAR was also detectable in cfDNA and was approximately 2-fold lower than PB. There were two outliers, both with ALL. Patient 1 had no detectable CAR at D9 with refractory disease. Patient 2 had CAR copies >3 SD above the mean at D8 and experienced grade 3 CRS requiring ICU. The patient achieved a complete and ongoing response >12 months.

The mean level of CAR at the early timepoint was higher in patients with DLBCL achieving a CR (6622 copies/µg (95% CI 0–13391)) compared to <CR (1452 copies/µg (95% CI 0–4280)) although not statistically significant. CAR persistence was detected in all 9 samples tested at day ≥100 (3 ALL, 6 DLBCL), 7 in complete response and 2 with PD.

Conclusion: We present the first results of Tisagenlecleucel CAR-T kinetics in an Australian cohort of patients. CAR was quantifiable in both PB and cfDNA samples using a ddPCR assay. This is anticipated to be a useful ancillary test to aid in clinical management.

H085

Paraneoplastic dermatomyositis with Non-Hodgkin's Lymphoma: two rare presentations

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Title:
Paraneoplastic dermatomyositis with Non-Hodgkin's Lymphoma: two rare presentations

Abstract:
Inflammatory myopathies, namely dermatomyositis(DM), are relatively rare autoimmune disorders, with the cardinal manifestation of systemic proximal myopathy and variety of cutaneous lesions. While these disorders are not uncommonly paraneoplastic phenomenon, association with Non-Hodgkin's Lymphoma (NHL) is less frequent and even rarer with primary mediastinal B-cell lymphoma (PMBL), with disease pathobiology not well understood.

We describe two rare cases of DM with occult NHL with significant diagnostic and management challenges, in 6 years of tertiary centre experience of numerous NHL cases.

CP*, 67-year-old gentleman presented with twenty kilograms weight loss over two months with a photosensitive violaceous rash, progressive proximal myopathy and raised creatinine kinase with skin biopsy consistent with DM. His management initially compromised of pulse methylprednisolone and intravenous immunoglobulin. Subsequent PET scan screening for occult malignancy with difficult disease control, demonstrated FDG avid paraaortic lymphadenopathy. Nodal and bone marrow biopsies confirmed Stage IV diffuse large B-cell lymphoma. He was offered R-CHOP chemotherapy regimen with eventual complete remission of his NHL and DM.

VG**, 44-year-old gentleman presented with a diffuse confluent rash over his upper body, progressive myopathy and dyspnoea over few months. His initial skin biopsy was most consistent with DM and TIF1gamma antibodies on myositis panel. With progressive dyspnoea, CT chest showed an irregular thymic mass that was surgically excised with histopathology concluding PMBL (thymic). Following recovery from post-operative complications, he was commenced on high doses of prednisolone and DA-R-EPOCH chemotherapy protocol, limited by management of sepsis. Despite a post-operative PET scan demonstrating no residual FDG avid lesions, the protracted hospitalisation has been complicated by progressive proximal myopathy, bulbar involvement with dysphagia and concerns for cardiac disease with recurring episodes of supraventricular tachycardia despite a structurally normal cardiac assessment after his fourth cycle of chemotherapy.

These two cases elucidate the diagnostic and management challenges in these rare entities.

H086

Nonagenarian Hodgkin Disease- A case report in the real world.

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Aim: Hodgkin lymphoma in nonagenarians is a rare event. Treatment options are not well defined in literature. This case report suggest a successful way to control the disease with minimal treatment.

Method: A 95 year old lady presented with abdominal pain, lethargy and reduced appetite. Further investigations were performed and the PET/CT scan revealed FDG avid infradiaphragmatic lymphadenopathy. A CT guided mesenteric lymph node biopsy showed classic Hodgkin lymphoma and staged as IIA. She received a patient tailored protocol of Brentuximab (1.8 mg/kg) and Dacarbazine (375 mg/m2). DVA approved her financial cost of the treatment.

Results: The aim of treatment was to improve her symptoms and better the quality of life with minimal complications. This chemoimmunotherapy was administered during COVID-19 pandemic. She tolerated once a month chemotherapy approach and achieved PET-CR after 6 cycles of treatment. She developed bilateral pneumonia after cycle 2 and responded to broad spectrum antibiotics. A total of 8 cycles were administered. She participated in the Cancer Fatigue Rehabilitation Program during the course of her chemotherapy. She now lives independently with minimal support.

Conclusion: Brentuximab and Dacarbazine (monthly) can be considered as a well-tolerated regimen along with early rehabilitation in Nonagenarian Hodgkin Lymphoma.

H087

Dose-Adjusted-EPOCH-R is a safe and well tolerated regimen in advanced stage double-hit lymphoma

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Aim: Double-hit high grade B cell lymphoma (HGBL) represents an aggressive subset of lymphoma with inferior prognosis with standard dose chemotherapy. Controversy remains whether more intensive chemotherapy such as DA-EPOCH-R (dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin and rituximab) provide better outcomes in this cohort. The aim of this research was to review consecutive cases of double-hit HGBL treated with DA-EPOCH-R at our institution in comparison to available literature to assess survival, feasibility and safety in a real-world outpatient setting.

Method: We conducted a retrospective study of 13 consecutive double-hit HGBL patients treated with DA-EPOCH-R at our tertiary institution in a primarily outpatient setting. Primary endpoints included complete response (CR), event-free survival (EFS) and overall survival (OS). Survival analysis was performed using the Kaplan-Meier method, with categorical data compared using 2x2 contingency tables with Fisher's exact test. Further descriptive analysis included adherence, tolerability and peak dosing level achieved.

Results: CR rate with DA-EPOCH-R in double-hit HGBL was 82% in our cohort. Median EFS and OS duration was 46 months (95% CI: 24-69 months) and 58 months (95% CI: 37-80 months) respectively. This is lower than published phase 2 data with a highly selected patient population [1], as this older and less fit cohort did not achieve higher dose escalation.

One patient discontinued DA-EPOCH-R due to toxicity and there were no treatment or infection-related deaths during the study. Patients had a median of 1 admission during treatment with no delays in therapy required.

Conclusion: This study suggests that DA-EPOCH-R is a well-tolerated outpatient regimen for double-hit HGBL in a real-world setting and should be considered for initial treatment in medically fit patients. Further prospective studies are warranted to confirm these findings.

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H088

Haemophagocytic Lymphohistiocytosis and Intravascular Large B-Cell Lymphoma: Hidden Partners in Crime

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Case: 63-year-old Caucasian male collapsed and was treated as septic shock, requiring vasopressors. He had a two-month history of generalised weakness, fevers up to 40C, sweats, unintentional weight loss of 20kg with hepatosplenomegaly.

Initial Investigations:

Haemoglobin 60-75g/L	Fibrinogen 7.5 g/L
Platelet count 60-70x109/L	Peak ferritin level 15900ug/L
CRP 150-200mg/L	Extensive septic and autoimmune screen non-contributory
Triglycerides 4.0 mmol/L	

He was treated as adult-onset Still's disease due to a transient arm rash and lack of an alternative diagnosis. High dose prednisolone and weekly methotrexate yielded some clinical improvement. An initial bone marrow biopsy was not diagnostic but a second performed after clinical deterioration showed florid haemophagocytosis consistent with haemophagocytic lymphohistiocytosis (HLH) (6 of 8 diagnostic criteria fulfilled). Dexamethasone and etoposide (HLH-94 protocol) commenced with resolution of fevers.

Other Investigations:

- PET scan (pre-steroids): FDG-avid pituitary gland without significant lymphadenopathy.
- MRI Pituitary (post-steroids): Mildly enlarged pituitary gland.
- Pituitary axis testing: Marked secondary hypothyroidism and secondary hypogonadism. Remaining pituitary work-up normal.

Subsequent random skin biopsies confirmed the diagnosis of intravascular large B-cell lymphoma (IVLBCL) as the likely trigger for the HLH (Figure 1). Treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone is planned.

Discussion: The presence of HLH and hypopituitarism in the context of an FDG-avid pituitary gland prompted further investigation into a link between both rare conditions. Lymphoma was considered in the differential as it is a common cause of HLH and IVLBCL has a predilection for endocrine organs. There are two case reports describing a similar clinical picture (1, 2), advising random skin biopsies as a non-invasive method of establishing the diagnosis of lymphoma. This is crucial as treatment strategies are significantly different (3).

Conclusion: IVLBCL should be considered in HLH without obvious triggers especially if there is suggestion of endocrine organ involvement.

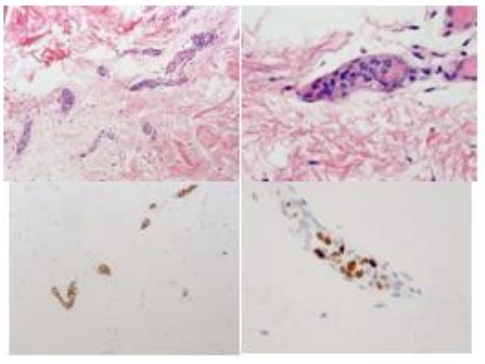

Figure 1A-D (Left to Right): The sections of skin show a proliferation of large pleomorphic lymphocytes, with irregular nuclear contours, variably apparent nucleoli, and minimal eosinophilic to clear cytoplasm situated in thin-walled lymphovascular spaces (Fig. 1A x 100 magnification and 1B x 400 magnification). Immunohistochemistry confirms the B-cell lineage with positive labelling for cd20 (Fig. 1C x 100 magnification) and a high mib-1 proliferative index (Fig. 1D x 400 magnification) in keeping with Intravascular large B-cell lymphoma.

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H089

Clinical characteristics of Australian treatment-naïve classical Hodgkin Lymphoma (cHL) patients from the Lymphoma and Related Diseases Registry (LaRDR)

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Aim: To describe baseline characteristics and current treatment patterns in Australian patients with cHL entered into the LaRDR from the first 5 years.

Method: Patients aged ≥16yrs, in the LaRDR with histologically proven treatment-naïve cHL were identified from Jul 2016 to Feb 2021. Nodular lymphocyte predominant Hodgkin Lymphoma was excluded due its distinct pathological, clinical, and prognostic features, and treatment regimens as compared to cHL. Clinical data analysed include baseline characteristics and treatment regimen, using descriptive statistics.

Results: 430 eligible patients were identified. Median age was 36yrs. 36% of patients were ≥45 yrs and 21% were ≥ 60 yrs. 45% of patients were female. 36% of patients were Stage I – IIA (early disease), 60% were Stage IIB – IV (advanced disease). ABVD was the most common therapy for both early- (93%) and advanced disease (45%), and 50% of patients with early disease also received radiation therapy. Other baseline characteristics will be presented in a table at the conference. These include proportion of cHL subtype, Hasenclever score and further details of treatment regimen by disease stage.

Conclusion: This is the largest analysis to date of Australian 'real world' data on patients with treatment-naïve cHL, and their baseline clinical characteristics are similar to those reported in international cohorts[1,2]. Understanding these characteristics will assist in application of results of international trials to Australian patients, and description of current therapeutic trends will also help design future trials. Further longitudinal data is needed to assess outcomes of current treatments and more information on clinical outcomes for these patients will be presented at the conference.

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H090

Real world management of Lymphoma and Related diseases in Australia: The first five years of the Lymphoma and Related Diseases Registry (LaRDR).

Prof Stephen Opat[1,9] *Ms Gayathri St George*[1], *Dr Cameron Wellard*[1], *Ms Eliza Chung*[1], *Dr Leanne Berkahn*[2], *Prof Chan Cheah*[3], *Dr Michael Dickinson*[4], *Prof Maher Gandhi*[5], *Dr Pratyush Giri*[6], *A/Prof Eliza Hawkes*[7], *Dr Anna Johnston*[8], *Dr Colm Keane*[5], *Dr Luke Wang*[9], *A/Prof Zoe McQuilten*[1,9], *Prof Stephen Mulligan*[10], *A/Prof Dipti Talaulikar*[11], *Prof Judith Trotman*[12], *Prof Erica Wood*[1,9],

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Aim: To describe 'real world' outcomes of patients with lymphoid cancer enrolled in LaRDR, a national clinical quality registry.

Method: Patients are registered on LaRDR prospectively. Clinical and treatment data are collected at baseline, then treatment and follow up data collected at 6, 12, 24-month intervals. All patients registered between January 2016 and March 2021 were included in this analysis. Demographics and lymphoma subtype are presented as numbers and percentages for categorical variables and median and interquartile range for survival analysis.

Results: 3834 patients were entered, representing 10% of all incident[1] cases in Australia. Median age at diagnosis was 65y with 36% >70y; 59% were male. Histological diagnoses included; Diffuse large B-cell lymphoma (35%), follicular lymphoma (17%), other B cell non-Hodgkin lymphoma (15%), Hodgkin lymphoma (13%), chronic lymphocytic leukaemia (8%), T-cell NHL (6%), mantle cell lymphoma (4%), and post-transplant lymphoproliferative disorder (2%). ECOG PS at presentation was 0-1 in 89% and 2-3 in 10%. With 12-month median follow-up, median overall survival (OS) for the entire cohort was 53 months, the 2-year progression-free survival and OS varies significantly by diagnoses (Table 1). Complete data for treatment, and initial response was available in 80% and 85%, but only 56% at 12-month review; data collection and follow-up are ongoing.

Conclusion: This is the largest report on Australian lymphoma patient demographics, histological subtypes, and prospectively collected outcomes to date. Baseline patient characteristics and frequency of lymphoma subtypes are comparable with reports from other registries. Further information on treatment and outcomes by subtype will be presented. Clinical registries such as LaRDR are valuable resources to evaluate disease epidemiology, patient demographics, patterns of care and outcomes, and to inform patient care, including for patients with rare subtypes where clinical trials are not feasible.

Table 1 Progression-free and overall survival by lymphoma diagnosis

Diagnosis	2-year PFS (95% CI)	2-year OS (95%CI)
Hodgkin lymphoma	79% (72%-84%)	96% (92%-98%)
T-cell non-Hodgkin lymphoma	48% (38%-58%)	57% (48%-66%)
Diffuse large B-cell lymphoma	71% (68%-75%)	72% (68%-76%)
Follicular lymphoma	69% (63%-75%)	93% (90%-96%)
Mantle cell lymphoma	55% (40%-68%)	78% (66%-86%)
Other B cell non-Hodgkin lymphoma	75% (69%-80%)	85% (79%-89%)
Post-transplant lymphoproliferative disorder	70% (38%-88%)	80% (40%-95%)
Chronic lymphocytic leukemia	76% (66%-84%)	91% (84%-95%)

- ***Reference*** *Australian Institute of Health and Welfare. (2019). Cancer in Australia 2019. Canberra: AIHW.*

H091

Human Herpesvirus-8 associated Multicentric Castleman disease with Kaposi sarcoma in a HIV-negative patient

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Introduction: Human Herpesvirus-8 (HHV-8) associated Multicentric Castleman disease with Kaposi sarcoma (KS) is a rare clinical entity. In HIV-positive individuals, dysregulated angiogenesis and up-regulation of viral cytokines is induced by HHV-8 and precedes KS. The pathogenic role of HHV-8 and interleukin-6 in HIV-negative patients is unclear.

Case: An 85-year old, HIV-negative female presented with steroid-responsive, idiopathic autoimmune haemolytic anaemia (AIHA). She was re-admitted two months later with B-symptoms and generalised lymphadenopathy. An excisional axillary lymph node biopsy demonstrated CD20-negative plasmablasts, spindled epithelioid cells with positive immunohistochemistry staining for HHV-8 and abnormal vascular proliferation consistent with HHV-8 MCD with KS. HHV-8 viremia (Ct value: 28) was present. Bone marrow and peripheral blood flow cytometry identified an abnormal NK/T cell population; the absence of bimodal TRBC1 antibody expression suggested an underlying low grade clonal process. Next generation sequencing is pending.
Intravenous methylprednisolone 250mg daily for 3 doses, followed by prednisolone 1mg/kg and rituximab 375mg/m^2 every 3 weeks with liposomal-doxorubicin (20mg/m^2) were administered. Valganciclovir (2.5mg/kg twice daily) was commenced in the setting of HHV-8 viremia. Treatment continues with ongoing clinical response.

Discussion: MCD and HHV-8 associated KS is a rare disease with clinical experience derived from limited prospective data in HIV-positive patients. The pathogenic role of HHV-8 in KS appears to arise through up-regulation of inflammatory genes. Viral proliferation has been linked to host immunodeficiency, in particular impaired T-lymphocyte function. Promising clinical responses have been noted with rituximab, cyclophosphamide and doxorubicin with adjunctive antiviral therapy. We postulate the presence of an abnormal T-cell clone (and perhaps steroid treatment for AIHA) resulted in immunosuppression allowing clinically significant HHV-8 proliferation.

Conclusion: Understanding the immune dysregulation and the interaction between three distinct but inter-related clinical entities; HHV-8, MCD and KS is required in order to achieve more targeted therapeutic strategies.

Disclosure of Interest Statement:
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H092

An Australian single-centre experience of immune effector cell associated neurotoxicity syndrome (ICANS) in patients treated with commercial tisagenlecleucel for diffuse large B cell lymphoma (DLBCL)

Dr Hannah Rosenfeld[1,2], *A/Prof Michael Dickinson*[1], *Dr Mark Dowling*[1], *Dr Adrian Minson*[1,2], *Ms. Nicole O'Leary*[1], *Dr Roberts Atvars*[1,2], *Dr Ashish Bajel*[1], *Prof Constantine Tam*[1], *Dr Arian Lasocki*[1], *Dr Charles Malpas*[1,2], *Prof Tomas Kalincik*[1,2], *Prof Simon Harrison*[1], *Dr Mary Ann Anderson*[1,2]
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Title: An Australian single-centre experience of immune effector cell associated neurotoxicity syndrome (ICANS) in patients treated with commercial tisagenlecleucel for diffuse large B cell lymphoma (DLBCL)

Aim: Here we report the incidence and characteristics of ICANS, a poorly understood and potentially devastating complication of chimeric antigen receptor T (CAR-T) cell therapy[1,2,3] in the largest cohort of Australian patients with DLBCL treated with commercial tisagenlecleucel.

Method: Individuals treated at the Peter MacCallum Cancer Centre who received commercial tisagenlecleucel for DLBCL from April 2019 to February 2021 were identified from our patient database (HREC 2016.305) and a retrospective review of their record was undertaken.

Results: 31 patients were identified. The median age was 68 (range 42-81) and the median number of prior treatments was two (range 1-5). 25/31 (80%) had CRS; with ten patients requiring at least one dose of tocilizumab. Two patients (6%) experienced ICANS, with clinical details below.

Patient 1 (69M) had Grade 2 CRS managed with one dose of tocilizumab. On day 14 he developed Grade 3 ICANS, characterised by drowsiness requiring intubation. MRI demonstrated two small recent infarcts. Cerebrospinal fluid (CSF) demonstrated 34 lymphocytes and raised protein 1.75g/L and no malignant cells. Electroencephalograms (EEG) demonstrated generalised slowing without epileptiform discharges. He was managed with intravenous steroids and prophylactic antiepileptics, with subsequent improvement in his conscious state.

Patient 2 (65F) had Grade 2 CRS and did not receive tocilizumab. She presented with attentional deficit on day 6 without other abnormalities (ICANS grade 1). She had a normal non-contrast CT brain. Symptoms resolved without specific management.

Conclusion: This study describes our single centre experience with ICANS in patients treated with tisagenlecleucel for DLBCL. Two patients (2/31; 6%) had ICANS. This is a lower incidence as compared with similar international cohorts[4]. The affected patients had no apparent differences when compared to the wider cohort such as disease bulk, bridging chemotherapy or prior neurological conditions. Prospective neurological and neuropsychological assessments may help to determine specific ICANS predictive factors in future.

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H093

Complete Metabolic Response of Refractory Plasmablastic Lymphoma with Daratumumab Combined with V-DA-EPOCH

Dr Ferenc Szabo[1], *Dr Kate Brotherton*[1], *Dr Selvein Thanarajah*[1]
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Aim: To observe whether the addition of daratumumab to a regimen of bortezomib with dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin (V-DA-EPOCH) achieves complete metabolic response in refractory plasmablastic lymphoma.

Method: A case report of a patient with stage 1 plasmablastic lymphoma of the maxillary sinus refractory to V-DA-EPOCH. Daratumumab was added to the initial regimen at a dose of 16mg/kg weekly for two cycles and then two weekly thereafter. Disease response was monitored with serial magnetic resonance imaging and positron emission tomography scans.

Results: Prior to commencing daratumumab, the patient had disease progression on V-DA-EPOCH. After one cycle of daratumumab plus V-DA-EPOCH the primary tumour demonstrated reduction in size. After 6 cycles of daratumumab plus V-DA-EPOCH, MRI and PET imaging confirmed complete metabolic response.

Conclusion: Plasmablastic lymphoma treatment is notoriously difficult given the aggressive nature of the disease and a limited body of evidence given its rarity. This case adds to our understanding of treatment of plasmablastic lymphoma specifically in refractory disease. It demonstrates that the addition of targeted CD38 therapy may improve outcomes for patients.

H094

Real world experience of Tisagenlecleucel in the treatment of Diffuse Large B Cell Lymphoma and Acute Lymphoblastic Leukaemia – A Single Centre experience

Dr Vinay Vanguru[1], *Dr Edward Abadir*[1,2], *Professor Christina Brown*[1,2], *Mrs Katrina Debosz*[1], *Mr Paul Malau*[1], *Dr Christian Bryant*[1,2], *Dr Scott Dunkley*[1,2], *Dr Liane Khoo*[1,2], *Dr Zlatibor Velickovic*[2,4], *Professor John Rasko*[2,3,4], *Professor Stephen Larsen*[1,2], *Professor Joy Ho*[1,2]
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Title: Real world experience of Tisagenlecleucel in the treatment of Diffuse Large B Cell Lymphoma and Acute Lymphoblastic Leukaemia – A Single Centre experience

Aim: Funding for Tisagenlecleucel for relapsed Diffuse Large B Cell Lymphoma (DLBCL) and relapsed Acute Lymphoblastic Leukaemia (ALL) was approved in 2020 in NSW. Here we report our centre's experience.

Method: Following treatment, disease assessment was performed using PET or bone marrow (as indicated) on Day 30, 90 and 180 post therapy. Cytokine release syndrome (CRS) and Immune Effector Cell Neurotoxicity (ICANS) were recorded as per ASTCT criteria.[i]

Results: We report 16 patients with DLBCL and 4 patients with ALL who had completed a Day 30 assessment at the time of reporting. Median ages for DLBCL and ALL patients were 67 and 24 years respectively. Number of prior lines of therapy were 2 for DLBCL and 3 for ALL. The overall CRS rate (Grades 1 and 2) for DLBCL and ALL was 69% and 75% respectively, with 25% Grade 2 CRS in both disease groups. No patient experienced CRS Grade 3 or above. Two patients (13%) in the DLBCL cohort had ICANS (Grade 2) requiring steroid management and both successfully recovered their neurological function within 48 hours of institution of therapy.

Overall response rate in DLBCL was 69% with complete response (CR) rate of 38%, while the CR rate in the ALL cohort was 100%.

Conclusion: CAR-T therapy in NSW is safe and effective in DLBCL and ALL with responses similar to the published data.

H095

Hairy Cell Leukaemia in Pregnancy: Two cases and a review of the literature

Dr Siobhan Walsh[1], *Professor Shaun Brennecke*
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To optimise outcomes for future pregnancies affected by hairy cell leukaemia (HCL) and ultimately improve maternal and fetal outcomes.

Method: We will discuss the patients' presentations eventuating to diagnosis, investigations carried out and management during the antenatal, intrapartum and postpartum periods.

Discussion: HCL is a rare haematological malignancy characterised by abnormal B cell lymphocytes causing pancytopenia and splenomegaly. It is uncommon in the general population, accounting for 1-2% of all leukaemias. It is particularly rare in young females, therefore there are limited cases reported of HCL complicating pregnancy.
First and second line treatment of HCL are medications that would usually be avoided in pregnancy: purine analogues and biological therapies. These are classified by the Australian Therapeutic Goods Administration as category D and C drugs respectively. Given these classifications, it is optimal to delay their use until after delivery. A review of the literature revealed twelve articles relating to HCL in pregnancy. All detailed treatment with purine analogues, interferons and/or splenectomy. This case review is important as it avoided the use of potential teratogens during the antenatal period. Successful supportive therapy (e.g. blood transfusions and prophylactic antibiotics) was initiated, and achieved term delivery in both cases.
The patients received differing antibiotic regimes although both were clinically stable, had normal neutrophil counts and did not have any risk factors for peripartum infection identified. The indication and rationale for the antibiotic treatment is unclear and is an area that requires further research.

Conclusion: HCL rarely complicates pregnancy, therefore there is limited reports in the literature to guide conservative management.
There is no standardised antibiotic protocol for these patients. This is an area that requires further research to optimise future management and ultimately improve maternal and fetal outcomes.

H096

Electronic FRAIL score as a prognostic indicator in elderly patients undergoing R-CHOP chemotherapy for newly-diagnosed DLBCL

Dr Jesse Zhang[1], *Dr Eileen Merriman*[2], *Dr Anna Elinder*[2], *Dr Merit Hanna*[2], *Dr Henry Chan*[2]
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Aim: Frailty is well correlated to worse outcomes and treatment tolerance in geriatric malignant haematology, making rapid frailty scoring systems important for patient risk stratification. The FRAIL score is a multifaceted electronic score which, when linked to an electronic medical records system, provides a quick and easy way to assess for pre-treatment frailty.

Method: 96 patients aged 70 and over at initiation of treatment who received at least one cycle of R-CHOP as first line chemotherapy for DLBCL at North Shore Hospital between 1 January 2010 and 31 December 2019 were included in the analysis. FRAIL scores were retroactively obtained from electronic patient records. Measured outcomes include progression-free survival (PFS), overall survival (OS) and need for dose adjustment or cessation of treatment due to treatment toxicity. Continuous variables were evaluated using the independent t-test and Mann-Whitney U test where appropriate, and categorical data was assessed using the Chi-square test.

Results: 96 patients were included in this study. The FRAIL score was predictive of PFS (HR 1.47, 95% CI 1.04 – 2.09) and OS (HR 1.51, 95% CI 1.06 – 2.15) even after adjusting for age (<75 vs >75) and IPI. The FRAIL score as a continuous variable was predictive of both OS (HR 1.51, 95% CI 1.07 – 2.12) and PFS (HR 1.48, 95% CI 1.05 – 2.08) on univariate analysis but not age >75, ECOG or IPI.

Conclusion: The FRAIL score is an effective prognostic tool strongly predictive of disease survival, more so than age, ECOG or IPI alone, in older patients undergoing R-CHOP chemotherapy for DLBCL. Once implemented in an electronic records system, it provides a quick and easy way for clinicians to quantify and risk-stratify the frailty of their patients.

H097

Design and implementation of a model of care for patients with germline predisposition to haematological malignancy and bone marrow failure syndromes

Dr Lucy Fox[1,2], *Ms Anna Jarmolowicz[1], Dr Mary Panjari[1], Professor Paul James[1,2], Professor Karin Thursky[1,2], Professor Jillian Francis[1,2], Dr Ashish Bajel[1,2], Professor David Ritchie[1,2], Dr Piers Blombery[1,2]*
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Aim: To describe the rationale, development, implementation and evaluation of a model of care (MoC) for patients with germline predisposition to haematological malignancy and bone marrow failure syndromes (BMF).

Method: We performed a nationwide physician survey (n=74) as well as semi-structured interviews with patients with BMF and patient advocates (n=9) with the aim of objectively identifying barriers to care. Comprehensive review of current evidence and treatment guidelines was performed. Results informed development of a MoC that is currently under evaluation using a hybrid implementation-effectiveness study – *The Evaluating Multidisciplinary Bone maRrow fAilure CarE (EMBRACE) study in Bone Marrow Failure and Related Disorders.*

Results: Physicians indicated a desire for affordable access to genomic testing and assistance with cascade testing of relatives, result interpretation and management advice. Patients described encounters with medical staff unfamiliar with their disease, leading to anxiety; and demonstrated a clear need for education both at initial presentation, in considering whether an underlying germline condition could be present and also following diagnosis, permitting disease specific management. Other challenges elicited included widespread difficulty in accessing genetic counselling and fertility advice, as were difficulties in transitioning from paediatric to adult care.

A MoC was subsequently developed which initially focuses on obtaining an accurate diagnosis with availability of genetic counselling and genomic testing followed by formally documented diagnostic formulations and management meetings involving referring clinicians. Disease specific management plans are determined, including suggestions for clonal evolution monitoring, surveillance for solid tumours and opportunity for further case discussion upon change in clinical state. This MoC is undergoing evaluation to determine acceptability and compliance with recommendations.

Conclusion:
We have developed an evidence-based MoC for the complex management needs of patients with BMF. This MoC will undergo iterative refinement as a result of continuous evaluation in order to provide optimum care.

H098

Case study: Management of Myelodysplastic Syndrome/Acute Myeloid Leukaemia in Shwachman-Diamond Syndrome

Dr Zhong Goh[1], *Dr Tennille Pelly*[1], *Dr Greg Seeley*[1]
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Background: Shwachman-Diamond Syndrome (SDS) is a rare inherited bone marrow failure syndrome. Major complications of SDS include Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML). This presentation details our local experience in managing a patient initially diagnosed with MDS, who later developed AML, on a background of SDS.

Case Presentation : A 43 year old male presented with 2 weeks of lethargy in the setting of SDS, which was diagnosed in childhood. His full blood count showed pancytopenia with a Hb of 68, WCC of 2.7, Plt of 39, ANC of 0.21 and peripheral blast count of 3% with predominant myeloblast. Bone marrow biopsy revealed 8% blasts with features consistent with Myelodysplastic Syndrome with excess blasts -1 (MDS-EB1). He had poor cytogenetics with del(5q), -7, +8, -10, -12, -13 and TP53 mutation (variant mutation frequency of 70%). Azacitidine was commenced whilst being worked-up for an allogeneic stem cell transplant (ASCT). He was not a transplant candidate due to liver cirrhosis, which was confirmed via imaging and biopsy. The aetiology of liver cirrhosis was likely due to fatty liver disease and excessive alcohol intake. He completed 9 cycles of Azacitidine before his MDS transformed into AML. Flow cytometry showed CD13+/CD33+/CD34+/CD117+/HLA-DR+/CD15neg/CD7var blast population accounting for 21% of total cells. He was started on Venetoclax and low-dose Cytarabine with palliative intent. He passed away 4 months after his AML transformation.

Discussion: SDS is rare, with an incidence of around 1 in 77,000. Affected individuals have strong predisposition of developing MDS and AML, often with poor cytogenetics. Treatment involves chemotherapy with the intent to proceed with ASCT. A barrier to ASCT is liver cirrhosis, which could be due to SDS-associated steatohepatitis as described in a few case reports.

Conclusion: For patients with SDS who develop AML, prognosis is poor. Azacitidine is a viable chemotherapy option in the treatment of high-risk MDS. However, ASCT should be attempted if there are no contraindications to transplant.

H099

Significant delay between onset of persistent cytopaenia and diagnosis of myelodysplastic syndrome

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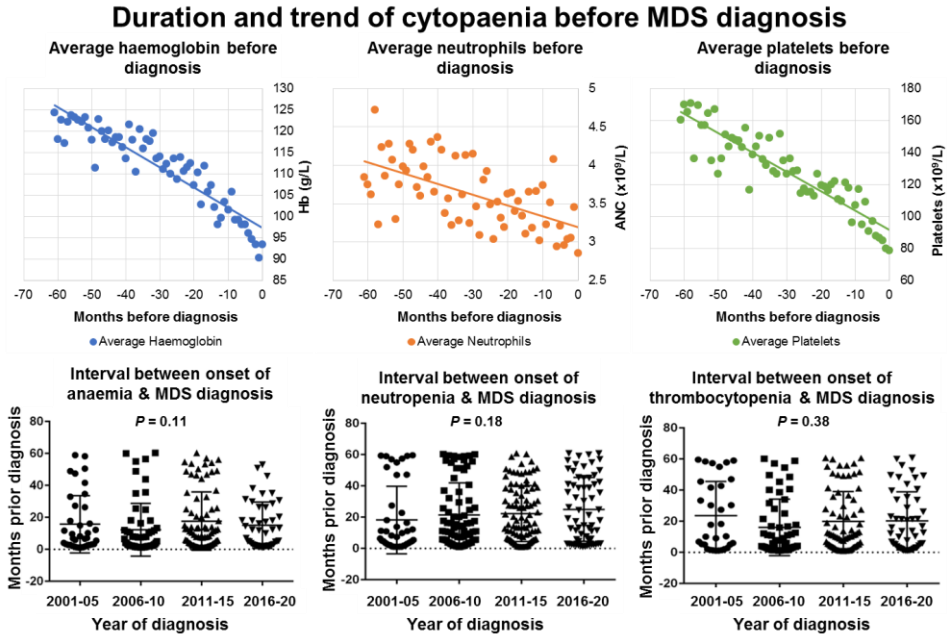
Background: Cytopaenias are one of the cardinal features of myelodysplastic syndrome (MDS) but a patient with gradually falling blood counts does not necessarily trigger a workup for MDS in clinical practice. Furthermore, there is scant literature assessing the interval between onset of cytopaenia and MDS diagnosis. As therapeutic options for MDS increase, earlier diagnosis could prevent morbidity, improve quality of life and survival. We aim to assess the kinetics and time interval of persistent cytopaenia *before* MDS diagnosis.

Methods: South Australian MDS (SA-MDS) registry includes serial blood counts of patients before and after MDS diagnosis. We assessed patients with persistent cytopaenia (haemoglobin<100g/L, platelets<$150x10^9$ and/or neutrophil<$1.8x10^9$) on at least two serial blood counts performed two weeks apart prior to diagnosis.

Results: Serial blood counts prior to MDS diagnosis were available in 77% (658/848) patients and 34%, 32% and 43% patients had persistent anaemia, thrombocytopenia and neutropaenia respectively. The median interval between persistent cytopaenia and MDS diagnosis was 15 (IQR 4.8-40.0) months. Critically, over the **last two decades** the **interval** between onset of persistent cytopaenia and MDS diagnosis **did not decrease.** Meanwhile, 30% (n=200) patients required 526 hospital admissions prior to MDS diagnosis with 54% being for management of infections and cytopaenia.
In addition, 5% (n=72) MDS patients also required multiple bone marrows (BM) to establish diagnosis. The median interval between first and diagnostic BM was 18.3 months (IQR 9.2-56.2). Meanwhile, 45% (32) patients progressed to AML (10%) or higher risk MDS (35%).

Conclusion: To our knowledge, this is the largest study of pre-diagnostic parameters in MDS patients demonstrating significant delay between onset of persistent cytopaenia and MDS diagnosis, and lack of improvement over the last two decades. Reasons include delayed referral and subjective morphological criteria. Hence, there is an urgent and unmet need to develop guidelines for early referral and workup.



H100

Quality of life of older frail myelodysplastic syndrome patients is poor and less likely to improve with hypomethylating therapy

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Aim: Myelodysplastic and acute myeloid leukaemia are one of the most common haematological malignancies of older people. We previously demonstrated that 30-40% of older MDS/AML patients are frail. Importantly, frail patients less likely to benefit from azacitidine and have significantly poor survival compared to their age matched fit patients (Molga et al, Journal of Geriatric Oncology 2020). This study aims to assess impact of frailty on quality of life (QOL) and compares the impact of HMA therapy on QOL of frail vs. fit older MDS patients

Method: Patients were recruited prospectively from 2014 to 2020. Patients aged ≥65 diagnosed with MDS (n=98), AML (n=29), t-MN (n=19) or MDS-MPN overlap (n=20) received comprehensive geriatric assessment and serial EORTC assessment. Patients who had instrumental activities of daily living (iADL), timed up-and-go (TUG) or mini-mental state examination (MMSE) assessment and at least one EORTC score were included in our analysis. Linear mixed-effects models, compound symmetry covariance structure and generalised estimating equations were used.

Results: Of 166 patients, 39% (64) had an abnormality in iADL, TUG and/or MMSE. 108 were male and 58 female and 39% (65), 49% (81) and 12% (20) were treated with supportive care, azacitidine and intensive chemotherapy respectively.

Global QOL (QL2) was poorer in iADL-dependant patients after adjusting for age, sex, IPSS-R, diagnosis, treatment and transfusion dependence ($p<0.0001$). iADL was a predictor of worse outcomes in functional domains. These patients reported worse symptom scores.

In azacitidine treated patients, QOL of iADL-dependent patients was poorer than independent patients ($p=0.04$) and did not improve over time.

Conclusion: Baseline comprehensive geriatric assessment predicts long term quality of life in MDS patients. iADL dependent patients have significantly poorer quality of life. Quality of life of frail MDS patients did not improve with HMA therapy.

H101

Clinical efficacy and safety of oral decitabine/cedazuridine in 133 patients with myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML)

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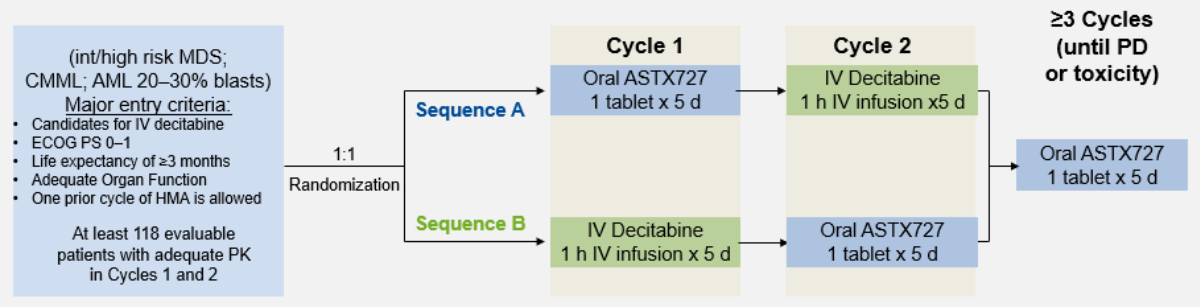
Aim: Confirm fixed dose combination (FDC) of oral decitabine/cedazuridine produces similar clinical activity vs. IV decitabine. Background: An oral FDC of 35 mg decitabine and 100 mg of CDA inhibitor cedazuridine has shown 99% (90% CI 93% to 106%) equivalent exposure to 20 mg/m2 IV decitabine in a randomized cross-over study(1). If oral decitabine/cedazuridine treatment produces similar clinical results its use may decrease the burden associated with chronic parenteral hypomethylating agent (HMA) therapy in MDS and CMML.

Methods: Randomized cross over design: 133 subjects treated in US or Canada.
Primary PK endpoint: decitabine AUC equivalence over 5 days of dosing. Efficacy endpoints: best response per IWG 2006, transfusion independence, OS, and safety. AEs were graded by CTCAE v 4.03.



Results: Patient Characteristics: median age 71.0 years; 65% male; 88%MDS/12%CMML; 43% either RBC or platelet baseline transfusion-dependent; 25% poor-risk cytogenetics, and 42% baseline BM blasts >5%. Best Response: CR in 29/133 patients (22%), mCR with HI:17% (without HI 16%), and HI: 7.5%, for an overall objective response (CR+mCR+HI) of 62%; 26% proceeded to transplant. With median follow up of 24.7 months, median OS had not been reached. Treatment-Emergent AEs (Grade ≥3 regardless of causality): thrombocytopenia (61%), neutropenia (58%), anemia (51%), febrile neutropenia (32%), leukopenia (25%), and pneumonia (18%), of patients treated with oral decitabine/cedazuridine (excluding IV decitabine cycle).

Conclusion: Efficacy and safety from oral decitabine 35 mg/ cedazuridine 100 mg daily for 5 days every 28 days are consistent with historical clinical data from standard IV decitabine 20 mg/m^2 daily for 5 days. Oral decitabine/cedazuridine is the only oral HMA with systemic exposure equivalent to its injectable drug. Further investigation of oral decitabine/cedazuridine in all-oral combination studies is warranted and underway.
References: 1) Garcia-Manero et al, ASH 201

H102

High burden of cardiac morbidity in myelodysplastic syndrome (MDS)

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Aim: Management of cardiovascular diseases in MDS patients is challenging due to thrombocytopenia and bleeding risk. We assessed burden and management of cardiac events in patients registered in South Australian MDS (SA-MDS) registry (n=910).

Results: During median follow up of 103 (95% CI from 58-170) months, 336 cardiac events were observed in 274/910 (30%) of MDS patients. Of the 336 cardiac events, 91 (27%), 123 (37%), 122(36%) were acute coronary syndrome (ACS), arrhythmia and heart failure (HF) respectively.

Of the total ACS events, 42% were non-ST elevation myocardial infarction (non-STEMI) while 22% were type II MI. Only 30% patients with ACS events had angiogram and only 12% patient had percutaneous coronary intervention (PCI) although 85% of patients who had angiogram had significant coronary disease. Only 33% and 40% of ACS events were treated with dual and single antiplatelet agents, respectively. Beta-blockers, ACE-inhibitors and statin were started in only 51%, 38% and 62% respectively.

The most common arrhythmia was atrial fibrillation (AF, 75%) and 37% of AF occurred in the setting of sepsis. CHADSVasc score was ≥2 in 89% of patients with persistent AF and would qualify for anticoagulation therapy, however only 31% and 17% AF events were treated with antiplatelet and anticoagulation therapy respectively. In terms of rate control 46% were on a beta blocker at the time of discharge with a further 33% on long term digoxin.

Majority of heart failure (HF) patients had ischaemic (40%), dilated (34%) or hypertrophic (20%) cardiomyopathy. At the time of discharge, only 42% and 41% were treated with beta blockers and ACEI/ARB.

Conclusion: One in three MDS patients suffer with acute cardiac events and management is suboptimal. Hence, there is urgent unmet need of developing guidelines for manging cardiac co-morbidities in MDS.

H103

Real-world review of Myelodysplastic Syndrome outcomes in an outer suburban hospital highlights significant challenges and an unmet need for better access to effective therapies

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Aim: The Northern Hospital(NH) is an outer suburban hospital in Melbourne that services surrounding suburbs and regional communities in the north of Victoria, with challenges of a rapidly growing migrant settlement and lower socioeconomic backgrounds. We sought to report the outcomes and identify treatment barriers of patients with myelodysplastic syndrome(MDS) at NH.

Method: Retrospective review of demographics, treatment and outcomes of all adult patients with newly-diagnosed MDS from Jan2010-Dec2020 at NH.

Results: 137 patients were identified. Median follow-up was 15months(mo). Median age at diagnosis was 78years. Majority were overseas-born (58%) and 35% required interpreter services. Patients lived a median of 10km(range 2-220) from NH and 20km(range 10-250) from Melbourne CBD. Overall survival(OS) according to International Prognostic Scoring System was 36mo for low, 29mo for intermediate-1, 19mo for intermediate-2 and 3.5mo for high risk(table 1), which was poorer than previously published cohorts1–3. 86(63%) patients have died at data cut-off: 29%(25/86) due to AML transformation, and 23%(20/86) due to infections. 83% patients were hospitalised at least once since diagnosis (median 3 admissions). 46(34%) received disease-modifying therapies. 33/54(61%) PBS-eligible patients received azacitidine; 9(17%) deteriorated rapidly after diagnosis and 5(9%) declined treatment. Clinical trial uptake was low: 5/12 referred declined due to travel distance. Comorbidity burden was substantial with a median Charlson Comorbidity Index(CCI) of 5(range 0-14), which significantly impacted on outcome: median OS was 51mo, 34mo and 13mo for CCI score of 0-3, 4-7 and >8 respectively (p=0.014). Azacitidine-eligible overseas-born patients had a trend to a lower OS (10mo vs 19mo, p=0.204) and higher CCI score (median 6 vs 3, p=0.059) compared to Australian-born patients.

Conclusion: Multiple factors such as increased comorbidity burden and limited access to trials likely contributed to poor outcomes in this outer suburban MDS cohort in Victoria. Better strategies are urgently needed to improve our care of this multicultural population.

Table 1: Comparison of outcomes between Northern Hospital and published MDS cohorts

	Northern Hospital			Median OS for comparison		
IPSS Group	*N*	Median OS	95% C.I.	Hui et al 2008[2] n=108	Berggren et al 2018[3] n=1139	Voso et al 2013[1] n=380
Low	*24*	36mo	(12-59)	72mo	67mo	NR
Int-1	*28*	29mo	(0-59)	57mo	31mo	57mo
Int-2	*31*	19mo	(11-26)	16mo	13mo	19mo
High	*7*	3.5mo	(2-5)	4mo	10mo	8.9mo
Overall	*137*	26mo	(14-38)	48mo	28mo	Not reported
Age (range)	78 (38-101)			70 (24-87)	75 (17-96)	71 (22-89)

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H104

Initial results of the MDSlink pilot: an Australian multi-site registry to understand the epidemiology, management and outcomes of myelodysplastic syndromes

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Aim - The aim of MDSlink is to collect and analyse diagnostic, treatment and clinical outcome data for Australians diagnosed with myelodysplastic syndromes (MDS). Here we summarise baseline data on the initial pilot cohort.

Method – MDSlink uses an opt-out consent model to maximise participation from all eligible patients (newly diagnosed MDS or AML <30% blasts on bone marrow biopsy). A minimum dataset and database were developed, and data collected at 4 pilot sites (Cabrini, Monash, Austin, Royal Adelaide).

Results – The initial MDSlink cohort consists of 123 participants. Median age is 74.6 years (range 66.5-80.4) with 39.8% female and 60.2% male.

Most patients had a diagnosis of MDS (80.5%) with 7.1% therapy-related myeloid neoplasm and 12.4% MDS/MPN (including CMML). Further classifications of MDS are shown in Table 1:

MDS classification	**Prevalence (%)**
MDS with excess blasts (MDS-EB)	47.2
MDS with multilineage dysplasia (MDS-MLD)	33.7
MDS with single lineage dysplasia (MDS-SLD)	9.0
MDS with ring sideroblasts (MDS-RS)	7.9
MDS, unclassifiable (MDS-U)	1.1
Other	1.1

Cytogenetic studies were available in 43.1% of participants. Of these patients, cytogenetics were normal in 64.2%, abnormal in 34.0% and unsuccessful in 1.9%.

Prognosis is calculated using IPSS and IPSS-R risk scores. Distribution by IPSS-R is shown in Table 2.

IPSS-R risk category	**Frequency (%)**
Very low	24.5
Low	29.6
Intermediate	21.4
High	16.3
Very high	8.2

Conclusion - The pilot was successful, demonstrating the feasibility of collecting comprehensive MDS patient data to describe the epidemiology of MDS in Australia, document and understand variation in care, support quality improvement activities, optimise clinical practice and evaluate resource utilisation. It also establishes the potential for MDSlink to expand to additional sites. Updated baseline and follow-up data from the initial cohort will be presented at the meeting.

H106

Significance of JAK2 V617F Allelic Burden in Myeloproliferative Neoplasms

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Aim: JAK2 V617F testing in our lab is performed using a quantitative real-time PCR based assay with FRET probes and melt curve analysis with an established sensitivity of 5%. Since mid-2018 our lab has routinely reported allelic burden rounded to the nearest 5%. This audit seeks to assess the relationship between JAK2 allelic burden and the phenotype of Myeloproliferative Neoplasms (MPNs) in our patient population.

Method: This was a laboratory based, retrospective Australian study using a historical catalogue request within the laboratory information system. All patients with a positive (n=165) or equivocal (n=11) JAK2 diagnostic test for the workup of a new haematological disorder during 2019 were assessed. Linear regression and ANOVA studies were performed.

Results: Of the 165 positive results, 85 patients were diagnosed with Essential Thrombocythemia (ET), 39 with Polycythaemia Vera (PV), 16 with Primary Myelofibrosis (PMF), 5 had a normal BMAT and 20 had other or unknown diagnoses. Eleven patients had equivocal results. Whilst not statistically significant, PMF had the highest allelic burden (median 58%, range 30-95%), followed by PV (median 45%, range 5-100%) and ET (median 16%, range 5-50%). Five patients with normal bone marrows and positive JAK2 demonstrated low allelic burdens (median 10%, range 5-12%). There was association between allelic burden and both white cell count (WCC) and haematocrit in PV, and allelic burden and both thrombocytosis and WCC in ET ($p<0.05$).

Conclusion: JAK2 allelic burden may aid in subclassification, with low allelic burden more likely in ET and normal marrows, however there is considerable overlap and the appropriate diagnosis needs to be carefully considered.

Evaluation of c-Kit D816V mutation testing in the investigation of mast cell disorders.

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Aim: C-Kit D816V mutation is found in multiple disorders ranging from monoclonal mast cell activation, systemic mastocytosis (SM) and aggressive myeloid disorders. We aim to evaluate indications for testing and clinical features to identify predictive factors.

Method: We identified 43 patients who underwent c-Kit mutation testing to investigate for SM, over a 2-year period (2019-2020) in Western Australia. Patient characteristics, clinical presentation and diagnostic results were compared between positive and negative groups.

Results: Forty-four percent of tests were positive. The average age was similar, approximately 51 years (range 6-75). Men comprised 58% positive cases, vs 37.5% negative. Indications for testing included anaphylaxis, rash and raised mast cell tryptase (MCT), however symptoms were found equally in both groups. Eighty-nine percent of those with the D816V mutation had raised MCT (>11.4 ng/mL), however, this was also raised in 75% of those without mutation. Median MCT were similar for c-Kit positive (22.2 ng/mL; range 6.3-193) and negative (17 ng/mL; range 3.2-30.6). Seventy-six percent of the cohort underwent bone marrow biopsy – abnormal mast cells meeting WHO criteria were found in 42% of c-Kit positive vs 12.5% of negative. Immunophenotyping detected abnormal CD25+ mast cells in 89% of c-Kit positive and 17% negative cases. Indolent SM was the most frequent diagnosis (52%), followed by cutaneous mastocytosis (26%). Aggressive SM accounted for 10% of cases, and SM-associated haematological neoplasm (AHN) accounted for 5%. The patients with aggressive SM/SM-AHN presented with C findings and high MCT (60-193 ng/mL).

Conclusion: The presence of symptoms was poorly predictive of c-KIT mutation in this cohort. Elevated MCT <3xULN was a poor discriminator, although high values >5xULN were associated with aggressive SM. While c-Kit myeloid disorders are rare, testing in situations of persistently elevated tryptase had high yield and we recommend a low threshold for mutation testing in this setting.

H108

Serious long-term complications of Ruxolitinib therapy in patients with Myelofibrosis.

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Aim: To describe the long term serious adverse events associated with Ruxolitinib therapy in Myelofibrosis patients.

Method: A retrospective cohort study was conducted of Myelofibrosis patients on Ruxolitinib between 2016 and 2021 treated by the haematology services in the Western Sydney Local Health District. Data was collected from patient records including hospitalisations, infection, cytopenias, secondary malignancy and other end organ complications. Descriptive statistics were used in the analysis.

Results: At abstract submission, twelve patients had been identified for the study. Median age at diagnosis=66 yrs. The range of duration of Ruxolitinib therapy was 2 - 96 months. 10 patients had 1 adverse outcome within 12 months of commencing Ruxolitinib. Five of these events required hospital admission. Infection was the most common adverse event (N=8) and cause for hospital admission with varicella zoster being the most common infection. Other adverse events included anaemia (N=4), worsening renal function (N=3) and secondary malignancy (N=2).

Conclusion: Our cohort analysis is consistent with the findings of the recent JUMP study demonstrating a similar rate and profile of adverse events. Although limited by cohort size, our study adds to existing data by analysing patients on a longer duration of Ruxolitinib therapy and capturing adverse events serious enough to require hospitalisation. These findings consolidate existing data to further guide clinical practice for prophylactic anti-infective therapy and secondary malignancy surveillance.

References :
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H109

Changes in blood counts related to tobacco smoking

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Aim: To determine patterns of abnormalities in full blood examinations (FBE) that mimic myelo- and lymphoproliferative neoplasms.

Method: Retrospective study of referrals to Townsville University Hospital haematology department between January 2017 and January 2020 for investigation of polycythemia, thrombocytosis, neutrophilia, monocytosis, and/or lymphocytosis. Data collected included patient demographics, smoking status, clinical information, investigations and diagnosis. Data were analysed for correlations between type, degree and pattern of cytosis with smoking status and final diagnosis.

Results: 395 patients were identified. Median age was 57yrs; 53% were female. Indications for referral were: neutrophilia in 143 (36%), polycythaemia in 124 (31%), thrombocytosis in 105 (27%), monocytosis in 105 (27%) and lymphocytosis in 90 (23%). 174 (44%) were current smokers. Final diagnosis was PRV in 10 (3%), ET in 16 (4%), CML in 4 (1%), CMML in 8 (2%) and other haematological malignancy in 17 (4%). Secondary causes were identified in 344 (87%) patients and smoking accounted for 143 (36%). 124 patients presented with polycythemia; 66 (53%) were smoking-related and a further 51 (41%) were secondary to other medical conditions (e.g. COPD, OSA). MPN diagnosis was negatively correlated with smoking status (8% vs 15%, p=0.031). The mean haemoglobin of smokers was higher than non-smokers (162.5g/l vs 154.5g/L, p=0.001). Of the 10 patients with a final diagnosis of PRV (including 3 with iron-deficient PRV without polycythemia), four were current smokers. Mean haemoglobin was higher in patients with diagnosed PRV compared reactive causes of polycythemia (191g/L vs 185g/L, p=0.013). All four smokers with PRV had an additional cytosis and/or myeloproliferative features on a blood film.

Conclusion: In investigation of cytoses, tobacco smoking can mimic MPN and can lead to additional expensive and invasive investigations. Degree of cytoses, film features and the presence of additional cytoses may aid in stratifying patients for further investigations.

H110

Differences in survival of patients with multiple myeloma in regional vs metropolitan regions: analysis of population data of an Australian local health district

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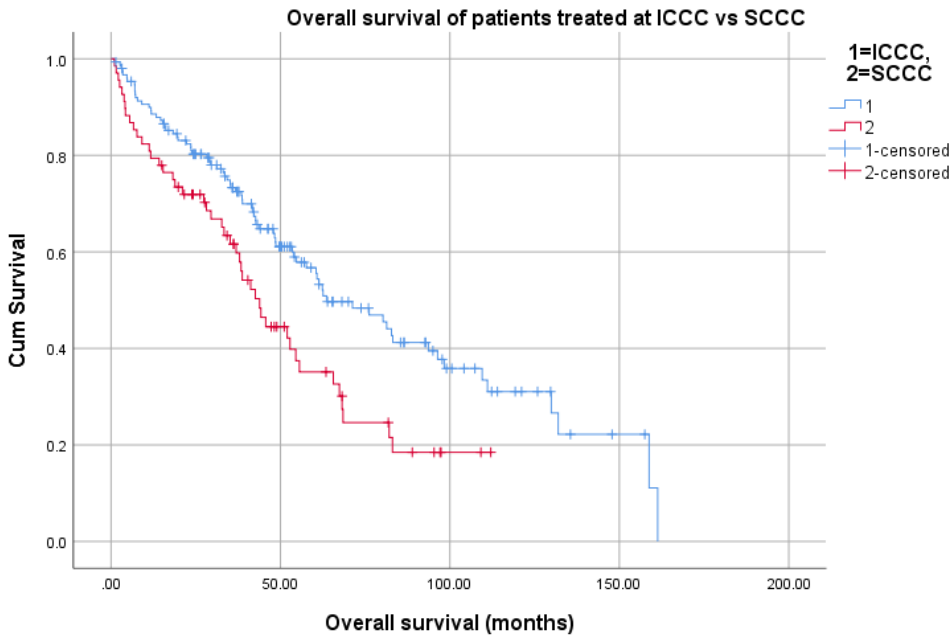
Aim: A number of studies have demonstrated poorer outcomes for patients with cancer who live in rural/regional areas compared to metropolitan areas. There is conflicting information on the effect of rurality on outcomes of patients with multiple myeloma, and limited information regarding the cause of this discrepancy. We aimed to determine if there was a discrepancy in the outcomes of patients with multiple myeloma treated in a regional cancer centre compared to a metropolitan cancer care centre, and identify the factors which contribute to this discrepancy.

Method: Retrospective analysis of demographic, treatment and outcomes of 238 patients newly diagnosed with multiple myeloma between 2002-2019 in the Illawara Shoalhaven Local Health District.

Results: Patients being treated in a regional cancer care centre had lower overall survival compared to those treated at a metropolitan cancer care centre (median OS = 63.6 months vs. 43.8 months, p=0.004) (Figure 1), and a trend towards lower progression-free survival (median PFS = 24.7 months vs. 19.8 months, p=0.228) despite treatment by the same group of hematologists. There was a lower rate of autologous transplantation for patients treated at a regional cancer care centre compared to a metropolitan cancer care centre (36% vs. 18%, p=0.007).

Figure 1



Conclusion: Survival differences between patients with multiple myeloma living in regional areas compared to metropolitan areas may be due to lower rates of autologous transplantation.

H111

Survey of myeloma patient expectations of the COVID-19 vaccination program.

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Introduction: The COVID-19 pandemic has continued to have a significant negative impact on global health outcomes. Vaccination programs have been implemented as a means to improve health outcomes but there have been uncertainties in the community regarding safety and efficacy of different vaccines, including patients with myeloma who are particularly vulnerable to COVID-19 infection with an increased mortality rate reported at 33%.

Aim: To prospectively survey patients with myeloma regarding their attitudes and concerns towards the COVID-19 vaccination program and to identify potential educational strategies or interventions that could be offered to support patients.

Method: 100 patients with multiple myeloma currently managed at the Royal Adelaide Hospital or The Queen Elizabeth Hospital participated in this survey. Descriptive statistics have been used for data analysis.

Results: 75% of patients reported they definitely intend to proceed with COVID-19 vaccination. 73% of these patients reported their decision was to reduce the risk of COVID-19 infection or the risk of serious illness associated with COVID-19 infection. Despite the majority of patients intending to proceed with vaccination, only 19% of all patients felt they had adequate information regarding the vaccination program. The majority of patients requested additional information in the form of either pamphlets (47%) or face to face discussion (32%). Of the 25% of patients that were not definitely proceeding with vaccination, 64% expressed concerns of the vaccination being rushed and wanted further safety information before proceeding.

Conclusion: Despite the current climate of concern and hesitation from the general public towards the COVID-19 vaccination program, the majority of our patients with multiple myeloma are planning to proceed with COVID-19 vaccination. Our cohort of patients expressed the need for more information and in response we have designed a COVID-19 vaccination information sheet for our myeloma patients, in addition to nursing and medical staff incorporating COVID-19 vaccination discussions as part of medical interactions.

H112

Talquetamab, a G protein coupled-receptor family C group 5 member D (GPRC5D) × CD3 bispecific antibody, in relapsed/refractory multiple myeloma (RRMM): Updated results of a phase 1, first-in-human study

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Aim: Evaluate talquetamab safety and preliminary antitumor activity in patients with RRMM.

Method: Eligible patients with RRMM who were intolerant to standard therapies received talquetamab IV (0.5–180µg/kg) or SC (5.0–800µg/kg) weekly or biweekly. Primary objectives were identification of the recommended phase 2 dose (RP2D; part 1) and evaluation of safety and tolerability at the RP2D (part 2). CRS was graded per Lee 2014, and response was assessed per IMWG criteria.

Results: As of Feb 8, 2021, 174 patients received talquetamab IV (n=102) and SC (n=72). 28 patients received the RP2D of weekly 405µg/kg SC (+10.0 and 60.0µg/kg step-up doses): median age was 61.5 years (range, 46–80) and median prior lines were 5.5 (range, 2–14; 100%/79% triple-class/penta-drug exposed; 71%/18% triple-class/penta-drug refractory; 86% refractory to last line; 21% with prior B-cell maturation antigen–directed therapy). No dose-limiting toxicities occurred at the RP2D in part 1. Most common AEs at the RP2D were CRS (79%; 4% grade 3), neutropenia (64%; 54% grade 3/4), anemia (57%; 29% grade 3/4) and dysgeusia (57%; all grade 1/2); 32% had infections (4% grade 3/4) and 7% had neurotoxicity (0 grade 3/4). 75% of patients dosed at the RP2D had skin-related AEs (0 grade 3/4), including 18% with nail disorders. ORR at the RP2D in 24 response-evaluable patients was 63%, 50% ≥VGPR; 9/17 (53%) evaluable triple-class refractory and 3/3 (100%) penta-drug refractory patients responded. Median time to first confirmed response at the RP2D was 1.0 month (range, 0.2–3.8); responses were durable and deepened over time (median follow-up 6.2 months [range 2.7–9.7+]). At the RP2D, exposure was maintained over the maximum EC_{90} target level, and consistent T cell activation was seen.

Conclusion: At the RP2D of weekly 405µg/kg SC, talquetamab showed a high response rate and was well-tolerated in patients with RRMM.

High dose melphalan and carfilzomib (Mel-Car) autologous stem cell transplantation in relapsed/refractory multiple myeloma patients: A single-centre experience.

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Aim: Bortezomib has been safely combined with melphalan autologous stem cell transplant (ASCT) conditioning with possible greater efficacy than melphalan alone.[1] Carfilzomib, a second generation proteasome inhibitor has a distinct structure and mechanism of action compared to bortezomib and has demonstrated efficacy in the relapsed/refractory (R/R) setting.[2] This study aims to evaluate the safety and efficacy of high dose melphalan and carfilzomib (Mel-Car) ASCT in R/R MM patients.
Methods: A retrospective case note audit identified 18 R/R MM patients who underwent a Mel-Car ASCT at the Peter MacCallum Cancer Centre and Royal Melbourne Hospital between March 2018 and November 2020. Data collected included patient and disease characteristics, toxicity data and post-ASCT response with bone marrow MRD assessment by flow cytometry (sensitivity 10^{-5}).
Results: Patient characteristics and disease response are included in Table 1. All patients had carfilzomib as part of the induction therapy. Twelve patients had a previous ASCT while 6 were refractory or had a suboptimal response to bortezomib and had upfront Mel-Car ASCT. Fifteen patients had melphalan 200mg/m^2 conditioning and three had 140mg/m^2. Carfilzomib was given at a dose of 56/m^2 on D-3 and D+2. Median time to neutrophil engraftment and platelet engraftment was 11 and 11 days respectively. There was no transplant related mortality. Three patients had infective complications, 7 required total parental nutrition, 1 fluid overload, superficial VTE and ICU admission respectively. Twelve patients (66%) achieved MRD negativity 2 months post-ASCT, 5 positive and 1 unavailable. Fourteen patients received consolidation and/or maintenance chemotherapy (carfilzomib n=9, lenalidomide n=4, thalidomide, n=1). Median follow up time was 19 months and six patients (33%) had progressive disease since ASCT.
Conclusion: Our experience suggest that carfilzomib can be safely combined with melphalan as a conditioning regimen for ASCT in R/R MM patients with high response and MRD negativity rates post-ASCT.

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Table 1 Patient characteristics and disease response

Variable	n
Sex	
M	12
F	6
Median age at transplant	64 (47 -75)
Myeloma subtype	
IgG	9
IgA	6
IgM	1
Light chain	1
Non-secretory	1
Cytogenetics/FISH	
High risk	2
Standard	12
Not available	4
Induction response prior to Car-Mel ASCT	
CR	4
VGPR	7
PR	6
PD	1
Response 2 months post-ASCT	
sCR	11
CR	1
VGPR	4
PR	1
No change/stable disease	1

H115

Imaging modalities in the evaluation of newly-diagnosed myeloma: a retrospective audit

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Background: The initial management of myeloma is dependent on accurate detection of bone lesions, a cardinal feature of myeloma. Cross-sectional imaging (CT, MRI) have been demonstrated to have increased sensitivity for myeloma lesions[1], which is reflected in International Myeloma Working Group (IMWG)[2] and the British Society for Haematology[3] guidelines.

Aim: To review concordance in Wellington Regional Hospital, New Zealand, with IMWG recommendations on imaging in monoclonal plasma cell disorders. Secondary aims included review of imaging patterns by referral source, rate of bone disease detected at diagnosis, time to pathologic fracture, imaging findings, initial treatment, and bisphosphonate adherence.

Method: A single centre retrospective audit using data from Wellington Regional Hospital, encompassing suspected myeloma cases between 2016 and 2020. Cases were identified from electronic medical records. Data was retrospectively collected from electronic medical records, and analysed with descriptive statistical analyses.

Results: 91 patients with suspected myeloma were included in this analysis, with a median age at diagnosis of 68 years (range 36–90).

Our audit included 79 patients with myeloma, 7 with smouldering myeloma, 3 with plasmacytoma, and 2 others.

We found that the initial imaging modality at diagnosis was skeletal survey in 52% of cases, and cross sectional imaging in 46% (CT in 43%, MRI in 3%). Patients received recommended imaging workup in only 33% of cases, with 12 patients receiving skeletal survey as their only initial imaging. Patients were more likely to have complete imaging if they presented with fracture (42%) or bone pain (53%), compared with no bone symptoms (17%).
Conclusion: Our audit demonstrates an unacceptably high rate of skeletal survey use in the initial investigation of myeloma, which may lead to late recognition and treatment of myeloma. This provides an impetus to improve access to cross-sectional imaging in monoclonal plasma cell disorders.

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H116

Bortezomib, cyclophosphamide and dexamethasone (VCD) as upfront treatment for systemic AL amyloidosis: experience from two Australian Amyloidosis services, and comparison to the ANDROMEDA study

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Aim: *Data regarding outcomes in systemic AL amyloidosis (AL) patients in Australia is lacking. We sought to audit patients characteristics and outcomes in two amyloidosis services within Australia when treated with VCD as frontline therapy.*

Method: Patients diagnosed with AL between 2017 to 2020 were identified via electronic medical records at Eastern Health (EH) and the Fiona Stanley Hospital (FSH). Patient demographics, treatment and outcomes were collected and analysed.

Results: 75 patients were diagnosed and treated with VCD as upfront therapy for AL amyloidosis.

Median age was 65 (range 33-84), and 68% (n=67) were male. 74% had cardiac, 55% renal involvement, with 35% of patients having more than two organs involved. Revised Mayo Staging was: I = 44%, II 25%, III 34%, IV 27%. Renal stage was I, II, and III in 58%, 34% and 8% respectively.

Frontline treatments were: Bortezomib/cyclophosphamide/dexamethasone (VCD) in 75 (76%); VCD and daratumumab in 2 (2%); lenalidomide based in 4 (4%); cyclophosphamide/dexamethasone in 6 (6%) and melphalan based in 4 (4%). Three patients did not receive treatment.

Haematologic response data was available in 94 patients. 29 (31%) achieved a complete response, 23 (24%) a very good partial response, and 28 (30%) a partial response corresponding to an overall response rate of 85%.

Median follow-up was 28 months for the cohort. At last follow up 34 patients have died. Median progression free survival was 18 months and median overall survival was not reached for the cohort. 16% of patients died within six month of diagnosis.

Conclusion: VCD is the most common treatment for AL amyloidosis. Clonal response rates are similar to those seen in Andromeda. Early mortality remains significant particularly for those with cardiac disease. Early institution of daratumumab may improve clonal response rates and patient survival.

Bortezomib, cyclophosphamide and dexamethasone (VCD) is effective first-line therapy for systemic AL amyloidosis, but early mortality remains high: the "real-world" Australian experience, and a case for the addition of daratumumab

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Aim: The ANDROMEDA study highlighted the benefit of adding daratumumab to VCD as upfront treatment of systemic AL amyloidosis (AL). Data regarding outcomes of AL patients in Australia is lacking. We sought to audit patients characteristics and outcomes in two amyloidosis services within Australia when VCD is used as firstline therapy in AL.

Method: AL patients diagnosed between 2017 to 2020 were identified via electronic medical records at Eastern Health and the Fiona Stanley Hospital. Patient demographics and outcomes were collected and analysed. Patients who received daratumumab with VCD were excluded.

Results: 84 patients were diagnosed and treated with VCD as upfront therapy for AL, four were excluded due to daratumumab co-administration.

Median age was 65 (range 33-84), and 66% (n=53) were male. 74% had cardiac, 52% renal involvement, and 35% of patients having more than two organs involved. Revised Mayo Staging was: I = 13%, II 24%, III 33%, IV 29%. Two patients had end-stage renal failure (ESRF) at diagnosis.

Complete clonal response were achieved in 25 (31%), very good partial responses in 23 (29%) and partial responses in 23 (29%), corresponding to an overall response rate of 89%. Cardiac responses, defined as reduction in NT proBNP by >30%, was observed in 42% of patients with heart involvement.

Median follow-up was 28 months. Five patients progressed to ESRF. 28 patients have died, eight of sudden cardiac death. 16% died within six month of diagnosis. Median progression free survival was 18 months; median overall survival was not reached.

Conclusion: VCD is effective upfront therapy for AL. Our clonal and organ response rates with VCD are better than those reported in the ANDROMEDA study. However, they remain inferior to those of VCD with daratumumab. Early mortality remains significant, particularly those with cardiac disease. Early institution of daratumumab may improve clonal response rates and patient survival.

H118

Daratumumab is well tolerated and significantly deepens clonal responses in patients with systemic AL amyloidosis

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Aim: Daratumumab has been reported in the 40 patient Phase II French AmyDara trial (Rousell et al, Blood, 2020) to be effective therapy in relapsed/refractory systemic AL amyloidosis (AL). We sought to confirm these findings with our local experience at the Victorian and Tasmanian Amyloidosis Service.

Method: AL patients with suboptimal clonal responses to prior therapy or relapsed disease subsequently treated with daratumumab were identified from medical records. Demographic and clinical information was collected, including age, best clonal response to daratumumab, and major toxicities. A suboptimal response was defined as achieving less than a VGPR (dFLC <40mg/L).

Results: Since 2019, eleven AL patients received daratumumab. All received prior bortezomib, cyclophosphamide and dexamethasone (VCD) as frontline treatment. Ten patients were treated for suboptimal clonal responses to prior therapies, one for relapsed disease. Of the ten suboptimal, eight received daratumumab as second-line and two as third line.

Median age was 63 (range 52-75), Male : Female 9:2. Revised Mayo Staging patients: I – one; II – four; III – two; IV – three.

Best post-daratumamab clonal responses thus far are CR – 4; VGPR – 4, PR – 2. One Revised Mayo Stage IV patient died of sudden cardiac death after two daratumumab infusions, but had already achieved a minor response.

The majority of first infusions were associated with minor infusion reactions. One patient experiencing fluid overload requiring increased diuretics after their first infusion, otherwise no significant toxicities were observed.

No patients have relapsed or had organ progression. Eight remain on daratumumab, and two ceased therapy after two years of treatment as per the compassionate access agreement.

Conclusion:
In AL amyloidosis, daratumumab was well tolerated with excellent clonal response, no progression of organ disease and should be considered the “rescue” treatment of choice for AL patients with suboptimal clonal response to frontline therapy.

H119

Reduction in absolute iFLC and dFLC is associated with prolonged major organ deterioration progression-free survival in newly diagnosed AL amyloidosis patients receiving VCd with or without daratumumab: results from ANDROMEDA

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Aim: Daratumumab plus bortezomib, cyclophosphamide, and dexamethasone (VCd) significantly improves outcomes in patients with systemic light-chain (AL) amyloidosis. ANDROMEDA (NCT03201965) assessed the impact of achieving reduced absolute involved free light-chain (iFLC) and the difference (dFLC) between iFLC and uninvolved FLC on major organ deterioration progression-free survival (MOD-PFS) as a key secondary endpoint.

Method: Patients with newly diagnosed AL amyloidosis with ≥1 involved organ, cardiac stage I-IIIA, eGFR ≥20 mL/min, and absent symptomatic multiple myeloma were randomly assigned (1:1) to receive daratumumab+VCd or VCd. Patients received subcutaneous bortezomib, oral/intravenous cyclophosphamide, and oral/intravenous dexamethasone for six 28-day cycles. Subcutaneous daratumumab was administered once weekly (Q1W; Cycles 1-2), Q2W (Cycles 3-6), and Q4W thereafter for up to 24 cycles. Disease evaluations occurred Q4W (Cycles 1-6) and Q8W thereafter, until major organ deterioration, death, study completion, or withdrawal. Primary endpoint: overall hematologic complete response (CR). Deep hematological response criteria: iFLC ≤20 mg/L and dFLC <10 (regardless of FLC ratio). MOD-PFS was defined as death; cardiac deterioration requiring transplant/left ventricular assist device/intra-aortic balloon pump; end-stage renal disease requiring hemodialysis/transplant; or hematologic progression.

Results: Overall, 388 patients (median age, 64 years) received daratumumab+VCd (n=195) or VCd (n=193). Between-group baseline characteristics were balanced. Involvement of ≥2 organs occurred in 65%: heart (71%), and kidney (59%); 23%, 40%, and 37% had cardiac stage I, II, and IIIA, respectively. Median treatment duration was 9.6 (daratumumab+VCd) and 5.3 months (VCd). Median follow up was 11.4 months. Daratumumab+VCd vs VCd had strongly favorable rates of deep hematological responses by all criteria (hematologic CR, 53% vs 18%; iFLC, 71% vs 20%; dFLC, 64% vs 31%) and longer MOD-PFS; the MOD-PFS was similar across all hematological response criteria.

Conclusion: Daratumumab+VCd increased deep hematologic response rates and prolonged MOD-PFS in patients with newly diagnosed AL amyloidosis.

H120

Improved outcomes for myeloma cast nephropathy in the modern era: a single-centre experience over 8 years

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Aim: Historically, myeloma cast nephropathy (MCN) was associated with poor renal outcomes. We aimed to examine the haematological and renal outcomes in the contemporary era of plasma cell directed therapy.

Methods: We conducted a single centre retrospective observational study from January 2012 to June 2020. The diagnosis of MCN was either biopsy confirmed (BC) (n=13) or clinically diagnosed (CD) (n=13) (defined as acute kidney injury with eGFR <30 mL/min/1.73m^2 and involved serum free light chains (iSFLC) >500 mg/L at diagnosis). Baseline characteristics at diagnosis, and haematological and renal responses were analysed.

Results: Twenty-six patients were identified. Treatment administered was: bortezomib in 18 patients, thalidomide in four, carfilzomib in two and melphalan/prednisolone in two. After a median follow-up of 27 (IQR 20-54) months, 50% died. These were older (81 (77-85) versus 65 (61-72) years still alive; P=0.01). Seventeen patients (65%) achieved complete (CR) or very good partial (VGPR) haematological response while 7 (27%) had partial response (PR) and 2 (8%) had stable/progressive disease respectively. Median eGFR at diagnosis was 12 (6-21) mL/min/1.73m^2. After therapy, the best median eGFR achieved was 47 (32-67) mL/min/1.73m^2 after 120 (63-167) days post-treatment, with all 6 dialysis-dependent patients achieving renal recovery. Patients with eGFR improving to above the median were more likely to have achieved an iSFLC of <20 mg/L (62% versus 0%; P<0.001). Of the 14 patients diagnosed in 2017-2020 (later era), there was a trend for shorter time from diagnosis to treatment (5 (4-10) versus 10(6-19) days; P=0.06). However, there was no difference in the best median eGFR achieved between the two eras (later: 44(31-68) versus earlier: 51 (34-62) mL/min/1.73m^2; P=NS).

Conclusion: Cast nephropathy with renal failure can be rescued with timely institution of myeloma therapy. Those with the deepest clonal responses have superior renal recovery. However, mortality remains high in older patients presenting with cast nephropathy.

H121

Analysis of plitidepsin (Aplidin) multiple myeloma access program in Australia

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Aim: To identify patient demographics that may identify potential responders to plitidepsin.

Method: Patients were enrolled on the plitidepsin compassionate access program by Australian hematologists. Baseline demographic data was entered into an online database at the time of patient registration. Unique patient identifiers were used to match patient baseline data with supply data. In the absence of key outcome measures (i.e. M-protein), supply data was used to infer duration of therapy.

Results: Between February 2019 and November 2020, 149 patients were enrolled on the access program. Median age was 68 (range 40-91); 23% ≥75 years; 54% male; 86.4% PS 0 or 1; median disease duration of 6.0 years (0.3-22 years); median of five prior lines (1-9), with 60.8% penta-refractory patients. The majority (85.2%) of patients were treated with plitidepsin (5mg/m^2) + dexamethasone (others in combination with a PI or IMiD). Fourteen percent of patients experienced ≥6 months of therapy. Key differences between this population and the overall population included fewer ≥75 years (14% vs 22.8%); PS 0-1 (100% vs 86.4%); . ≥SD as response to last therapy (81.6% vs 100%).

Figure 1: Duration of therapy (months)

3 months, 54%; ≥3 months, 45%; ≥6 months, 14%

Conclusion: The data presented as part of this analysis combined with the ADMYRE data highlight an important efficacy signal and proof of concept for plitidepsin, a molecule with a novel mechanism of action. Early identification of patients that would respond to plitidepsin remains a challenge. Although several studies have demonstrated higher expression of eEF1A2 on multiple myeloma cells when compared to normal plasma cells, a commercially available prognostic test is not currently available. Baseline demographic data did not provide a meaningful identifier for early responders.

H122

Results from a Phase-I dose-escalation study investigating clinical activity and safety of cevostamab (anti-FcRH5xCD3) in relapsed/refractory multiple myeloma (RRMM)

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Aim: To present results from an ongoing Phase I dose-escalation trial (NCT03275103) investigating safety and activity of cevostamab (anti-FcRH5xCD3 bispecific antibody) in patients with RRMM.

Method: Patients for whom no available established therapy is available, appropriate or tolerated received IV cevostamab in 21-day cycles. Risk of cytokine release syndrome (CRS) was mitigated by giving a single step-up dose (0.05–3.6mg) on Cycle (C) 1 Day (D) 1, with the target dose (0.15–132mg) given on C1D8 and D1 of each subsequent cycle.

Results: 51 patients were enrolled; 46 patients were evaluable for efficacy at cut-off (13 April 2020). Response to ≥3.6/20mg dose levels was observed in patients with high-risk cytogenetics, triple-class refractory disease, and prior exposure to anti-CD38 mAbs, CAR-Ts, or antibody-drug conjugates (ADCs). At cut-off, 6/15 pts had been in response for >6 months. Median safety follow-up was 6.2 months. 49/51 patients had ≥1 treatment-related adverse events (AE); the most common was CRS (74.5%): Grade 1, 39.2%; Grade 2, 33.3%; Grade 3, 2.0% (due to Grade 4 transaminase elevation). CRS was most common in C1 (38/51; 74.5%), and uncommon/absent in C2–17 (4/51; 7.8%). 84.5% of CRS events resolved within 2 days. 18/38(47.3%) patients with CRS received tocilizumab and/or steroids No treatment-related Grade 5 (fatal) AEs were reported. 2% of treatment-related AEs led to withdrawal of treatment. Maximum tolerated dose was not reached. Cevostamab PK appeared linear across the active dose levels tested, with the estimated half-life supporting the Q3W dosing regimen.

Conclusion: Initial data demonstrate that cevostamab has promising activity and manageable toxicity in heavily pre-treated patients with RRMM. Deep, durable responses were observed in patients with high-risk cytogenetics, triple-class refractory disease, and/or prior exposure to anti-CD38 mAbs, CAR-Ts, or ADCs. C1 single step-up dosing mitigated the risk of severe CRS and allowed escalation to clinically active doses.

H123

Cytogenetic Abnormalities in Multiple Myeloma can be detected by Imaging Flow Cytometry

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Aim: Chromosomal aberrations are prognostic indicators in multiple myeloma and generally detected by FISH analysis of 200 cell nuclei. Our aim was to assess whether “Immuno-flowFISH”, an automated imaging flow cytometry method that integrates immunophenotyping with FISH analysis can detect cytogenetic abnormalities in plasma cells.

Method: Bone marrow and blood samples from 17 cases of myeloma were analysed. After red cell lysis, samples were immunophenotyped with fluorescently conjugated antibodies to CD38 and CD138 and hybridised with FISH probes for 17p12 (TP53), 4p16 (FGFR3), 11q13 (MYEOV), 14q32 (IGH) and chromosome 17 centromere (CEP17). Nuclei were stained and up to 50,000 cells acquired on the Amnis ImageStreamX mark II imaging flow cytometer. Digital imagery and numerical data were assesed for FISH signals within immunophenotyped plasma cells.

Results: CD38/CD138-positive plasma cells ranged from 0.4 – 99% marrow cells with chromosome abnormalities in 10/17 cases. These were in 21 - 59% of plasma cells, or 0.2 – 51% of all cells. There were 2 cases with abnormal dual fusion signals for IGH and FGFR3 probes indicating t(4;14);IGH-FGFR3, and IGH and MYEOV probes consistent with t(11;14);IGH-MYEOV. Another 3 cases had 3 FISH signals for MYEOV or IGH indicating trisomy 11 and 14 respectively. Five cases had 1 FISH signal for 17p and two for CEP17, the pattern of del(17p). The plasma cells in the remaining 7 cases, and the CD38/CD138 negative cell populations in all cases had the normal 2-spot FISH signals for each probe analysed.

Conclusion: Imaging flow cytometry can detect significant chromosomal abnormalities, including translocations, hyperdiploidy and del(17p) in positively-identified plasma cells in myeloma. This high-throughput automated method analyses many thousands of immunophenotyped cells, does not require prior plasma cell isolation and had a limit of detection of <1% plasma cells. This novel approach will be validated on larger cohorts to verify clinical applicability.

H124

Venetoclax- Bortezomib, Cyclophosphamide, Dexamethasone (V-VCD) induction in Newly Diagnosed Transplant Eligible Multiple Myeloma (NDTE MM) – the AMaRC 18-01 trial

Dr Tishya Indran[1], *Dr Sridurga Mithraprabhu[2], Professor Simon Harrison[3], Ms Jacqueline Widjaja[1], Dr Sundra Ramanathan[4], Ms Flora Yuen[1], Professor Andrew Spencer[1,2]*
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Aims: In NDMM, to 1. define the overall response rates (ORR) and minimal residual disease (MRD) negativity at day 100 post autologous stem cell transplant (ASCT) with V-VCD 2. determine the impact of V-VCD on peripheral blood stem cell (PBSC) mobilisation, and 3. correlate V-VCD responses with the exRNA (liquid biopsy) transcriptome.

Method: A multi-centre study at The Alfred Hospital and Peter MacCallum Cancer Centre in Melbourne and St George's Hospital in N.S.W. A safety run-in of 3 patients received Venetoclax 400mg daily (Day 1-35) with Bortezomib 1.3mg/m2 subcutaneous, Cyclophosphamide 500mg oral and Dexamethasone 40mg (Days 1, 8, 15 and 22) for 4 x 35-day cycles. The Venetoclax was dose subsequently increased to 800mg daily. End points were ORR after induction and ASCT, adverse events (AE), MRD using 8 colour flow cytometry (Euroflow), PBSC and transplant outcomes and exRNA quantitation BCL-2, MCL-1, CCND2, CCND3, BAK1, BCL2L1 and MYC transcripts.

Results: 17 of a planned 45 patients were enrolled between 3/2018 and 9/2019 when the trial was halted by AbbVie due to increased infectious mortality with Venetoclax in the BELLINI trial [1]. The ORR (PR or better) with V-VCD after 4 cycles was 82%. Common AEs are shown below. The Venetoclax cohort required more PBSC collection days (p=0.0015), more plerixafor with/without cyclophosphamide (p= <0.0001) with a trend toward delayed neutrophil engraftment compared to a contemporaneous VCD-induced cohort. Post ASCT, ORR was 89% with 38% MRD negativity in the evaluable population. Non-responders demonstrated lower MCL-1 expression (p=0.012) and higher BAX/MCL-1 and BCL2/MCL-1 ratios (p= 0.05 and p=0.019) than responders at C1D8 when compared with baseline.

	Grade 1-2	Grade 3	Grade 4
Any adverse events	17 (100%)	9 (53%)	2 (12%)
Pain (generalized, specific site)	10	2	
Infection/fever	6	1	
GI (Diarrhea, constipation)	6	1	
Nausea/vomiting	7	0	
Neutropenia	2	3	2
Febrile neutropenia		2	

Conclusion: V-VCD induction for NDMM demonstrates high response rates with manageable myelosuppression but a potentially negative impact on PBSC mobilisation. Targeted exRNA transcriptomic evaluation may enable the early identification of V-VCD responders and warrants further evaluation.

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H125

Australian multiple myeloma projections to 2040: A rare cancer no longer?

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Aim: Multiple myeloma (MM) is the second most common hematologic malignancy in Australia but historically considered a rare cancer. While recent advances in treatment and diagnosis have improved survival, MM remains largely incurable with related health expenditure considerable. The study aimed to project incidence and mortality rates and estimate the numbers of cases and deaths to 2040.

Method: We projected MM incidence and mortality rates, standardised to the 2001 Australian population, using age-period-cohort models using national incidence and mortality data for 1982 to 2016. We estimated the future numbers of cases and deaths by applying the rates to the Australian Population Projections.

Results: From 2016 to 2040, the number of cases increased from 1,911 to 3,597 and deaths from 933 to 1,224. The age-standardised incidence rate for those age <70 was projected to increase in men from 4.0/100,000 to 4.5/100,000 and in women from 2.7/100,000 to 3.0/100,000 from 2016 to 2040. In the older age group (70+), incidence rates increased from 51.6/100,000 to 60.2/100,000 and in women from 32.7/100,000 to 35.7/100,000 over the same period. For mortality, the rates decreased over time for those <70, from 1.2 to 1.0/100,000 in men and 0.8 to 0.6/100,000 in women, and in those 70+, from 32.9 to 23.7/100,000 in men from 20.6 to 14.3/100,000 in women.

Conclusion: The number of MM cases and deaths will continue to increase as Australia's population ages. Projected incidence increases would result in growing demand for treatment and rising health expenditure. MM is considered a chronic cancer and as such requires and will continue to require prolonged and complex treatment and care. Building Australian evidence is a priority, particularly for prevention, early intervention and estimating the impact of novel therapies on the Australia population.

H126

Variable Clinical Presentation and Response to Therapy in Patients with IgM related AL Amyloidosis

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Aim: Immunoglobulin light chain (AL) amyloidosis associated with IgM monoclonal gammopathy is rare, accounting for 5% of AL amyloidosis. The clinicopathological features are distinct compared to non-IgM AL amyloidosis.

Method: We conducted a retrospective review of patients with IgM AL amyloidosis treated at three tertiary institutions in Australia. We describe the clinical presentation, disease features and outcomes.

Results: Seventeen patients were identified. Median age at diagnosis was 68 years (range 60-86), 53% were female. Organ involvement included kidney (41%), neurological (29)% and heart (24%). Lymph node involvement was present in 41%. Of 13 patients with bone marrow biopsy, 77% had a lymphoplasmacytic infiltrate. Of 6 patients tested, 5 had MYD88 L265P mutation detected. Light chain was lambda in 76%.
Twelve patients underwent therapy with various regimens including rituximab, cyclophosphamide and dexamethasone in 4, bendamustine and rituximab (BR) in 5, bortezomib-based in 1, melphalan and dexamethasone in 1 and single agent ibrutinib in 1 patient. One patient received autologous stem cell transplant after induction with CD. Of 11 evaluable patients, the overall response rate was 73% - complete response in 10%, very good partial response (VGPR) in 20% and partial response in 45%. The 3 patients achieving at least VGPR all received BR. The patient receiving ibrutinib achieved a 50% reduction in IgM monoclonal protein level after 3 months of therapy, although lambda light chain level remained unchanged. After median follow up of 39 months, 4 patients have died, with a corresponding 5-year overall survival of 66%.

Conclusion: Patients with IgM related AL amyloidosis typically present with renal and lymph node involvement and bone marrow biopsy revealing a lymphoplasmacytic infiltrate. Cardiac involvement appears less common than in non-IgM AL amyloidosis. Patients treated with regimens directed at lymphoplasmacytic clone appear to do well. Incorporating novel agents such ibrutinib requires further study.

H127

Outcomes of transplant ineligible patients with Multiple Myeloma treated in the contemporary era

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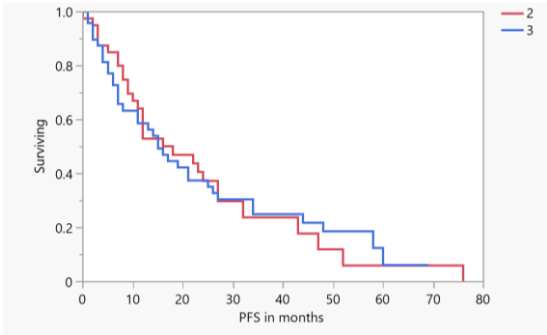
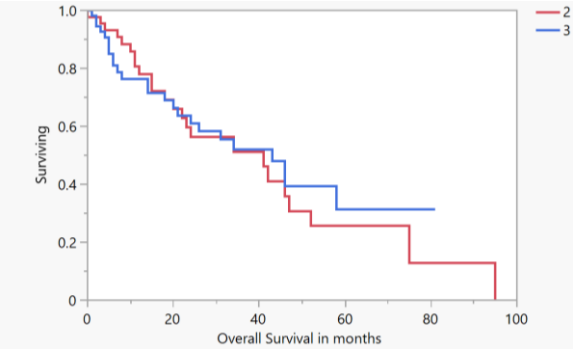
Aim: To assess the clinical presentation, treatment and outcomes of elderly, transplant ineligible myeloma patients.

Method: Patients diagnosed with multiple myeloma between 2013 and 2019 at two tertiary centres in Western Australia who were transplant ineligible were included in the study. Clinical features, treatment trends and survival outcomes were analysed.

Results: 102 patients were identified and included in the analysis. Median age was 76 years (range 65-91) and 51% were female. Features at diagnosis: Hb 104g/L (IQR 88-120), bone marrow plasma cells 40% (20-80 IQR), renal impairment 23% and lytic lesions 60%. ISS stage was available for 81 patients, stage 1 25%, stage II 32%, stage III 43% and 17% had high risk cytogenetics. Bortezomib based therapy was most common at 52%, followed by lenalidomide 24%. The most common triple regimen was bortezomib, cyclophosphamide and dexamethasone (VCD) 42% and most common doublet was lenalidomide and dexamethasone (RD) 21%. Overall response rate was 82%: complete response 13%, very good partial response 33% and partial response 36%. Median follow-up was 32 months with a median progression free survival (PFS) of 16 months and overall survival of 41 months. There was no difference in survival between doublet or triplet regimens or between the different agents, see figure 1.

Conclusion: The majority of transplant ineligible patients in our cohort were treated with bortezomib based regimens with use of lenalidomide based regimens increasing, reflecting drug approval trends in Australia. Although response rates are encouraging, the majority of patients progress within 2 years of diagnosis. There was no difference in survival outcomes between choice of novel agent and whether a triplet or doublet regimen was used. This may reflect better tolerability of doublet regimens in this population, a factor that needs consideration given the recent approval of the combination bortezomib, lenalidomide and dexamethasone in this cohort.





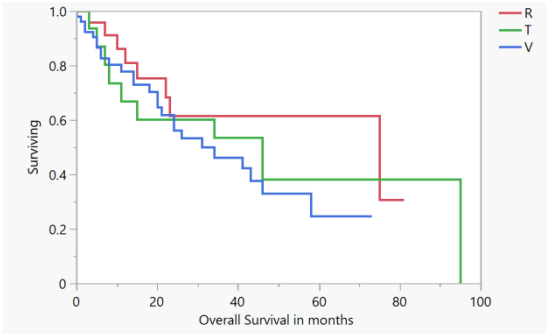


Figure 1. (A) Progression free survival, doublet versus triplet therapy, p=0.99
(B) Overall survival of doublet versus triplet therapy, p=0.8.
(C) Overall survival of lenalidomide (R) versus thalidomide (T) versus bortezomib (V), p=0.5.

H128

FISHing for Prognosis in MGUS

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Aim: Our study aims to explore the utility of cytogenetics and FISH results in the prognosis, prediction and risk stratification of patients with MGUS who may later develop MM.

Method: A retrospective clinical audit of the records of all MGUS patients who underwent FISH testing at the Molecular Medicine Department at John Hunter Hospital between the years 2009 and 2019 were reviewed and correlated with prognostic clinical data.

Results: A total of 86 patients with MGUS were identified, 10 of whom went on to develop MM. The presence of an abnormal free light chain ratio with a gain on long arm of chromosome 1 (gain1q) and deletion on short arm of chromosome 17 (del17p) were associated with a significantly shorter time to progression. Univariate and multivariate analysis of a risk stratification system based upon high risk features of del(17p), gain(1q), translocations t(14;16), t(4;14) and trisomies (i.e. gain of whole chromosomes) of odd numbered chromosomes was significant for a shorter time to progression compared to patients without these high risk features.

Conclusion: FISH studies provide important clinically relevant prognostic risk information in addition to free light chain ratios, level and type of M protein.

H129

Iberdomide (IBER) in combination with dexamethasone (DEX) and daratumumab (DARA), bortezomib (BORT), or carfilzomib (CFZ) in patients with relapsed/refractory multiple myeloma (RRMM)

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Aim: To report results from CC-220-MM-001 (NCT02773030), an ongoing phase 1/2 study evaluating MTD, RP2D, safety, and efficacy of IBER+DARA+DEX (IberDd), IBER+BORT+DEX (IberVd), and IBER+CFZ+DEX (IberKd) in RRMM patients.

Method: Eligible patients received ≥2 prior regimens in the IberDd and IberKd cohorts, and ≥1 prior regimen in the IberVd cohort, containing lenalidomide/pomalidomide, and a PI. All patients had progressed ≤60 days of last therapy. Escalating oral doses of IBER were given Day (D)1–21 of each 28-D cycle in the IberDd and IberKd cohorts, and D1–14 of each 21-D cycle in the IberVd cohort.

Results: As of Dec/14/2020, 34 patients had received IberDd, 24 IberVd, and 7 IberKd. Exposure to prior regimens was heterogeneous (Table); all patients were refractory to their last prior regimen. IBER doses ranged from 1.0 to 1.6mg. Median follow-up was 3.9 (0.1–20.7), 5.5 (1.2–18.0), and 5.1 (3.5–15.7) months, 15 (44%), 9 (38%), and 3 (43%) patients continue on treatment, and median cycles received were 4 (1–21), 7.5 (1–24), and 5 (3–16) with IberDd, IberVd, and IberKd, respectively. Hematologic grade 3–4 TEAEs of interest included neutropenia (63%), anemia (28%), and leukopenia (28%) with IberDd; neutropenia (29%) and thrombocytopenia (25%) with IberVd; and lymphopenia (57%) and neutropenia (43%) with IberKd. Neutropenia was managed with G-CSF. The overall response rate was 41% with IberDd, 58% with IberVd, and 57% with IberKd. Median time to response was 4.1 (4.0–12.0), 3.6 (3.0–13.1), and 4.1 (4.1–8.1) weeks, in the IberDd, IberVd, and IberKd cohorts, respectively. Median duration of response is 63.3 weeks in the IberVd cohort (not reached in the other cohorts). RP2D was determined at 1.6mg in the IberDd cohort; dose evaluation continues in the other cohorts.

Conclusion: In heavily pretreated patients with RRMM, IberDd, IberVd, and IberKd showed a manageable safety profile and promising efficacy, even among DARA- and BORT-refractory patients.

Table. Baseline characteristics and prior therapies

Characteristics	IberDd (n = 34)	IberVd (n = 24)	IberKd (n = 7)
Age, median (range), years	66 (40–77)	64 (47–81)	61 (36–69)
Time since initial diagnosis, median (range), years	8.0 (1.1–19.1)	7.1 (3.0–16.0)	7.7 (2.4–13.5)
ISS at study entry, n (%)			
Stage I	20 (58.8)	13 (54.2)	6 (85.7)
Stage II	9 (26.5)	9 (37.5)	0
Stage III	4 (11.8)	2 (8.3)	1 (14.3)
Presence of EMP, n (%)	7 (20.6)	4 (16.7)	1 (14.3)
Prior therapies, median (range)	4.0 (2–12)	5.5 (1–14)	6.0 (2–8)
ASCT, n (%)	29 (85.3)	21 (87.5)[a]	7 (100)
BORT, n (%)	33 (97.1)	23 (95.8)	7 (100)
CFZ, n (%)	24 (70.6)	11 (45.8)	4 (57.1)
LEN, n (%)	34 (100)	24 (100)	7 (100)
POM, n (%)	24 (70.6)	18 (75.0)	7 (100)
DARA, n (%)	18 (52.9)	19 (79.2)	7 (100)
Anti-BCMA, n (%)	2 (5.9)	2 (8.3)	1 (14.3)
IMiD agent-refractory,[b] n (%)	33 (97.1)	19 (79.2)	6 (85.7)
PI-refractory, n (%)	28 (82.4)	16 (66.7)	5 (71.4)
BORT, n (%)	14 (41.2)	10 (41.7)	4 (57.1)
CFZ, n (%)	21 (61.8)	8 (33.3)	4 (57.1)
Anti-CD38 mAb-refractory, n (%)	16 (47.1)	19 (79.2)	5 (71.4)
DARA, n (%)	16 (47.1)	18 (75.0)	5 (71.4)
Triple-class refractory,[c] n (%)	14 (41.2)	11 (45.8)	4 (57.1)

[a]4 patients received both autologous and allogenic stem cell transplant; [b]Defined as refractory to LEN or POM; [c]Defined as refractory to ≥1 IMiD agent, ≥1 PI, and ≥1 anti-CD38 mAb.

ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; BORT, bortezomib; CFZ, carfilzomib; DARA, daratumumab; DEX, dexamethasone; EMP, extramedullary plasmacytoma; IBER, iberdomide; IberDd, IBER+DARA+DEX; IberKd, IBER+CFZ+DEX; IberVd, IBER+BORT+DEX; ISS, International Staging System; IMiD, immunomodulatory drug; LEN, lenalidomide; mAb, monoclonal antibody; PI, proteasome inhibitor; POM, pomalidomide.

H130

Lenalidomide, bortezomib, dexamethasone (RVd) therapy in newly diagnosed, transplant eligible patients with multiple myeloma: A Harmonised Approach

Dr Georgia McCaughan

Aim: We proposed use of the GRIFFIN[1] RVd protocol for induction in transplant eligible patients. We aimed to analyse toxicity, dose modification, mobilisation statistics, response rates and survival in a real world population.

Method: All newly diagnosed, transplant eligible patients with MM prescribed VRd at 9 NSW sites are registered prospectively. Baseline patient and disease characteristics are collected. Toxicity, dose modification and response following induction; mobilisation statistics and response following transplantation and consolidation are collected. Disease and patient status are documented 6 monthly.

Results: At abstract submission (enrolment ongoing) 46 patients at 5 sites had been registered. Median age was 65 and 25 were male. 40/46 had a frailty score calculated (24 Mayo, 16 IMWG, 4 both) and 43/46 had a R-ISS (I in 16; II in 22; III in 6). 31/46 have completed induction. 5/31 had induction ceased prematurely due to toxicity. Dose reductions/cessation occurred for lenalidomide (8/31), bortezomib (8/31) and dexamethasone (3/31). Peripheral sensory neuropathy occurred in 13/31 (9 Grade 1; 3 Grade 2; 1 Grade 3) requiring bortezomib cessation in 2. 12 patients required hospitalisation during induction. Post induction response was CR in 3, VGPR in 19 and PR in 9/31. Transplant was not pursued in 2 patients, 28 patients have been mobilised. Median number of collection days was 2, unplanned plerixafor use occurred in 5 and 1 patient failed mobilisation. 21 patients have undergone transplantation. 8/14 patients with sufficient follow-up received consolidation.

Conclusion: Harmonisation of RVd treatment was feasible across the NSW sites. Neuropathy was seen in 13/31 patients requiring bortezomib cessation in 2. There was 1 mobilisation failure. Further evaluation is necessary to assess the toxicity, mobilisation data and response rates utilising this regimen in a real world.

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H131

Lenalidomide, bortezomib, dexamethasone (RVd) therapy in newly diagnosed, transplant ineligible patients with multiple myeloma: A Harmonised Approach

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Aim: We proposed use of the GRIFFIN[1] RVd protocol for induction in transplant eligible patients. We aimed to analyse toxicity, dose modification, mobilisation statistics, response rates and survival in a real world population.

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Conclusion:

Harmonisation of RVd treatment was feasible across the NSW sites. Neuropathy was seen in 13/31 patients requiring bortezomib cessation in 2. There was 1 mobilisation failure. Further evaluation is necessary to assess the toxicity, mobilisation data and response rates utilising this regimen in a real world.

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H132

Pharmacodynamic (PD) effects of dose and schedule of CC-92480, a novel cereblon (CRBN) E3 ligase modulator (CELMoD) agent, in patients with relapsed/refractory multiple myeloma (RRMM)

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Aim: To determine PD effects of CC-92480, a novel CELMoD® agent, in the phase 1 study (NCT03374085) investigating CC-92480 in heavily pretreated patients with RRMM.

Method: An adaptive Bayesian dose-escalation design was used to evaluate continuous dosing schedules of 10/14 days (d) ×2 and 21/28d, and intensive schedules of 3/14d ×2 and 7/14d ×2. PD changes were characterized by biomarker analysis from patients' peripheral blood (PB) and bone marrow (BM) aspirates (BMA), and included Ikaros/Aiolos levels in PB mononuclear cells by flow cytometry; CRBN, Ikaros/Aiolos, and ZFP91 expression by immunohistochemistry in BMA; weekly serum free light chain (sFLC) and soluble B-cell maturation antigen (sBCMA) levels; and effects on immune cells in PB. CC-92480 plasma exposures were also collected.

Results: The CC-92480 RP2D was selected at 1.0mg, 21/28d. Ikaros/Aiolos degradation was evident at all doses in BM plasma cells, and was dose-dependent in PB T cells (>80% at ≥0.6mg); at the RP2D, CC-92480 induced rapid, sustained decreases in sFLC and sBCMA. During drug holidays, substrate recovery was observed, with faster recovery at lower doses, and full recovery with ≥7d breaks. Increasing CC-92480 dose decreased B cells (>90% at ≥0.8mg in continuous schedules); T-cell proliferation increased 30—350%. At all doses and schedules, NK-cell proliferation peaked 1wk post-dose, and T cells shifted from naïve to effector phenotype and increased in HLA-DR, CD38, and ICOS. Regulatory T cells increased (90% at 0.8mg; 130% at 1.0mg). Higher percentages of proliferating CD3+CD4+ and CD3+CD8+ T cells were associated with clinical response at 1.0mg and more continuous schedules.

Conclusion: PD activity of CC-92480 was dose-dependent from 0.1–1.0 mg, and recovery was dose- and schedule-dependent. Degradation and recovery of Ikaros/Aiolos occurred with changes in PB immune cell subsets, suggesting dose and schedule can modify and optimize immune profiles, providing rationale for combining CC-92480 with immunotherapies.

H133

Causes of death in multiple myeloma in Australia: results from the Australian and New Zealand Myeloma and Related Diseases Registry

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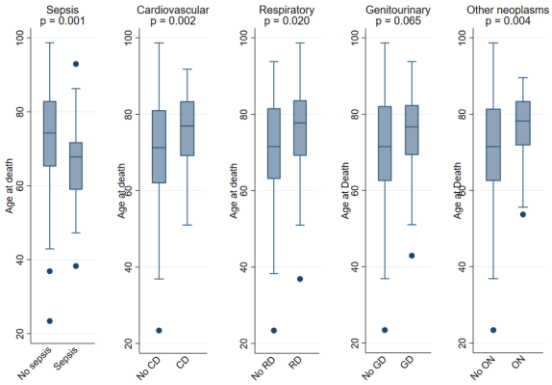
Aim: With novel treatments extending survival for multiple myeloma (MM), causes of death (COD) other than MM have increased relevance. We described COD in Australian patients with MM focusing on infection, as immunocompromise due to disease or anti-myeloma therapy is common.

Method: We evaluated patient characteristics for major COD categories of deceased Australian patients with MM registered in the Myeloma and Related Diseases Registry (MRDR, Feb 2013 - Sep 2020) using data from linkage with the Australian National Death Index (NDI). Major COD categories were determined using the General Record of Incidence of Mortality.

Results: Of 2289 Australian patients with MM on the MRDR, 591 were deceased, of whom 329 had NDI COD data. As expected, these 329 patients were significantly older (71 vs 67y), more frail (ECOG 2-4: 36 v 17%), with more severe disease (ISS = 3: 47 v 27%) at diagnosis than surviving patients. Median survival was 22 months, and MM was reported as primary COD in 90% of patients. When primary and other contributing COD were combined, the most common causes, after MM, were diseases of the circulatory (30%), genitourinary (22%), and respiratory (13%) systems; other neoplasms (14%), and infection (25%). Sepsis was reported in 41/82 (50%) of infections causing death, and pneumonia was most common (>25% of deaths from infection). Patients dying of sepsis (41/329) were younger than those without (68y [IQR: 59-72] v 74y [65-83], p=0.001); this contrasts with other major COD categories, where patients who died of a cardiovascular, genitourinary or respiratory disease, or other neoplasms, were diagnosed older than those without (Figure 1).

Conclusion: Despite availability of more effective therapies, the dominant primary COD in MM remains the disease itself. Of contributing factors, infection, particularly sepsis, in younger patients likely receiving more intensive therapies, is an area for potential therapeutic improvement.

Figure 1. Box plots show age at diagnosis for each of the COD groups compared to the rest of the cohort



H134

RVD (Revlimid, Velcade and Dexamethasone) as upfront treatment for newly diagnosed multiple myeloma: the initial "real world" experience at Eastern Health

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Aim: RVD has recently been listed for PBS-reimbursement for newly diagnosed multiple myeloma in Australia. We describe our initial experience with this novel triplet regime at Eastern Health.

Method: Patients treated with RVD were identified via pharmacy dispensing records. Demographic and clinical information was collected, including age, treatment regime, number of cycles administered, best response (per IMWG criteria), major toxicities and success/failure of PBSC mobilisation. Data was analysed in a descriptive manner.

Results: Fifteen patients received RVD induction since its PBS-listing in 2020. Twelve patients received full-dose RVD, whilst three patients received the RVD-lite regime. Median age was 65 (range 45-81). 5/15 patients were R-ISS Stage I, 9/15 R-ISS Stage II, 1/15 R-ISS Stage III.

Twelve of the thirteen patients who have completed ≥2 RVD cycles achieved haematological response: 1/13 CR, 4/13 VGPR, 7/13 PR, and 1/13 MR. Five patients have ongoing treatment, seven have completed RVD (Median number of cycles = 4, range 3-5) and proceeded to autologous transplantation.

Grade 3/4 toxicity was limited to three patients – one episode of septic shock requiring ICU admission, two episodes of severe rash (one biopsy confirmed DRESS). Both patients with severe rash were co-prescribed allopurinol and trimethoprim/sulfamethoxazole. Two patients ceased treatment due to toxicity.

Nine patients attempted PBSC mobilisation, typically after C3 RVD. Three patients failed G-CSF mobilisation and required repeat mobilisation with cyclophosphamide or plerixafor.

Conclusion: RVD is a generally well tolerated, effective treatment. Two cases of severe rash occurred patients co-prescribed allopurinol and trimethoprim/sulfamethoxazole, resulting in a unit policy to cease allopurinol before commencing trimethoprim/sulfamethoxazole. We also noted frequent failure of G-CSF alone PBSC mobilisation post RVD, which is being explored in a Melbourne-wide project.

H135

Up to 90% loss of plasma cells in bone marrow aspirates from patients with multiple myeloma: Implications on minimal residual disease (MRD) testing

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Minimal residual disease (MRD) using multicolour flow cytometry is an increasing important prognostication and surrogate marker in the management of multiple myeloma. Achieving MRD negative status can influence clinical decision for the need for further therapy. Currently, MRD testing is not readily available at local peripheral laboratories due to hardware and validation limitations.

As a laboratory quality assurance project, we investigated the stability of bone marrow biopsies of patients with multiple myeloma to assess the reliability or impact of referring MRD analysis at a centralised laboratory. Aliquots from up to 10 specimens with 10-90% plasma cells were freshly lysed, incubated and analysed with flow cytometry on the day of collection, and after 1 and 2 days. Viability of specimens were monitored with 7-ammoactunimycinD (7-AAD). Percentage of CD138+/CD38+ cells were gated, and 2 tailed t-test was used to determine statistical significance.

Significant reduction of plasma cells (n=7) were observed at day 1 (median reduction 67%, range 10-90%, p=0.001) and at day 2 (median reduction 71%, range 26%-90%, p<0.001). Median viability on day of collection, at day 1 and at day 2 were 90%, 97% and 96% respectively. The most significant specimen deterioration observed was only 13% viability reduction to 75% overall specimen viability. Mean fluorescence index (MFI) of CD38 was observed to decline consistently in all specimens, but MFI of CD138 was erratic.

This pilot study demonstrated the pre-analytical confounder secondary to delays in processing due to specimen transportation. Up to 1 log reduction of plasma cell percentage was observed, which implied potential compromise to the sensitivity depth and risk of false negative results. These findings indicate the need for prompt testing at local sites to ensure reliability, efficient couriers, or methods that stabilise the specimens to allow for delay in processing.

H136

In-class transition (iCT) from parenteral bortezomib-based induction to all-oral ixazomib-lenalidomide-dexamethasone (IRd) in multiple myeloma (MM) in the community-based US MM-6 study: analysis of factors impacting treatment duration with IRd

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Aim: US MM-6 is investigating *i*CT from parenteral bortezomib-based induction to all-oral IRd with the aim of increasing duration of proteasome inhibitor (PI)-based treatment and improving patient outcomes.

Method: As of 1-Jun-2020, 101 non-transplant-eligible newly diagnosed MM patients with ≥stable disease after 3 cycles of bortezomib-based therapy had been enrolled across 21 US community sites to receive IRd (≤39 cycles). Patient/disease-related characteristics were analysed in ongoing (n=40) and discontinued (n=61) patients, and by duration of treatment (DoT; ≤5 vs >5 cycles of IRd; n=30 vs n=70, excludes 1 ongoing patient with <5 cycles). Enrolment is ongoing.

Results: Median duration of PI-based therapy was 14 cycles (24 in ongoing patients; 9 in discontinued patients). Ongoing vs discontinued patients were younger at baseline (70% vs 44% aged <75 years), more commonly female (63% vs 39%), more frequently had stage I disease (38% vs 21%), had similar response rates to initial bortezomib-based therapy (≥very good partial response: 30% vs 33%), and less frequently had baseline renal/urinary (33% vs 41%) and cardiac (23% vs 34%) comorbidities. Among patients with overall PI-based therapy DoT ≤8 vs >8 cycles (including 3 cycles of bortezomib-based therapy), 57% vs 40% were aged ≥75 years, 60% vs 49% were male, 27% vs 37% had stage III disease, and 20% vs 13% had ECOG performance status 2; rates of key comorbidities were similar. Patients discontinued after ≤8 vs >8 cycles (n=30 vs n=31) due to progressive disease (17% vs 29%), toxicity/adverse events (20% vs 19%), patient request/decision/withdrawal (47% vs 26%), sufficient response (3% vs 13%), and other reasons (13% vs 13%).

Conclusion: Among this elderly, comorbid community MM population, discontinuation and shorter DoT were more common in elderly patients with key comorbidities, poor performance status, and >stage I disease. In conclusion, additional supportive care/management may enable these patients to benefit from longer-term PI-based treatment.

A retrospective analysis of the impact of VRD induction on peripheral blood stem cell collection for plasma cell myeloma

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Aim: Triplet therapy with bortezomib, lenalidomide and dexamethasone (VRD) was listed on the Pharmaceutical Benefits Scheme in June 2020, superseding the combination of bortezomib, cyclophosphamide and dexamethasone (VCD) as frontline therapy for plasma cell myeloma (PCM). However, lenalidomide is known to negatively affect peripheral blood stem cell (PBSC) collection. We aimed to assess the impact of VRD induction on the success of stem cell harvest by conducting a multi-centre retrospective analysis.

Method: We reviewed all transplant eligible patients with PCM from two Queensland tertiary institutions who underwent first attempt at PBSC mobilization with cyclophosphamide/GCSF between January 2020 and February 2021. The co-primary endpoints were rates of mobilization and collection failure (defined as peripheral blood CD34+ $<10x10^6$/L on day 1 of apheresis and total CD34+ yield $<2.0x10^6$/kg). Secondary endpoints included the number of apheresis sessions required, the CD34+ yield, the use of plerixafor rescue and days to engraftment. Statistical analysis was performed using Fisher's exact test and 2-sample t-test

Results: There were 77 patients in total; 38 patients received VRD and 39 received VCD. In the VRD group seven patients failed to mobilize compared with two in the VCD group (*p=0.087*). Four VRD patients failed to collect compared with one VCD patient (*p=0.20*). There was no difference in the total CD34+ yield (9.85 $x10^6$/kg for VRD versus $8.75x10^6$/L for VCD, *p=0.34*). There were seven VRD patients who required three apheresis sessions compared with no VCD patients. Rescue plerixafor use was higher in the VRD group (four versus two). There was no difference in time to neutrophil and platelet engraftment (*p=0.27* and *p=0.80*, respectively).

Conclusion: Whilst VRD induction is associated with a trend towards higher mobilization failure rates, increased number of apheresis sessions and increased use of plerixafor, our data shows that the majority of patients can be successfully collected with chemo/GCSF.

Carfilzomib induced microangiopathic haemolytic anaemia: a single cohort retrospective analysis

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Aim: To determine the incidence of carfilzomib induced microangiopathic haemolytic anaemia (MAHA) in multiple myeloma patients treated in our centre. Furthermore, to determine if subclinical cases of carfilzomib induced MAHA occur in addition to rare cases of thrombotic microangiopathy (TMA). Finally, to characterise any subclinical episodes and note any predisposing factors.

Method: A retrospective analysis was performed at a single centre examining all carfilzomib treated patients with multiple myeloma from 2010 to 2019. Patients were excluded if they received less than 3 cycles of carfilzomib. From a total 46 patients, 31 were eligible. Data was obtained including presence of schistocytes on blood film, haemoglobin, platelet count, haemolytic markers and renal function at multiple time points.

Results: Out of 31 patients, 11 (35.5%) had at least one subclinical episode of MAHA during carfilzomib treatment. 2 of these patients later developed carfilzomib induced TMA with severe end organ injury. 5 of the 11 patients (45%) with subclinical MAHA had associated transient acute kidney injury with no other cause, consistent with unrecognised TMA.

Subclinical episodes of MAHA secondary to carfilzomib were associated with older age (mean 72 vs 64 years old in unaffected group, p=0.02) and concurrent infection in 3 of 11 cases.

Conclusion: Carfilzomib induced TMA is an established rare adverse event. However this study demonstrates that subclinical episodes of MAHA can occur in a substantial portion of carfilzomib treated patients. Older age and concurrent infection are risk factors. Episodes can be associated with renal dysfunction with no other cause, indicating unrecognised TMA. Although less severe than overt TMA, these unrecognised episodes may cause chronic renal injury with prolonged carfilzomib use. Subclinical MAHA may indicate underlying susceptibility to carfilzomib and risk of future TMA. Patients receiving carfilzomib should be monitored for haemolysis and renal dysfunction. Ongoing therapy should be re-evaluated in patients that develop subclinical MAHA

Carfilzomib (CFZ) use among patients with relapsed/refractory multiple myeloma in the Asia Pacific (APAC) region: an interim analysis from a prospective, real-world study

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Aim: To describe utilisation of KRd and Kd in routine clinical practice in APAC, including treatment patterns, patient profile and reasons for discontinuation.

Method: This prospective, single-arm cohort study recruited adults with RRMM who received ≥1 dose of CFZ in either a combination or monotherapy regimen and had received ≥1 prior line of MM treatment prior to CFZ initiation. Medical history, patient characteristics and clinical data will be collected at baseline and throughout the 2-year observation period or until death, withdrawal of consent or loss of follow-up. Follow-up data will be collected through chart reviews every 3 months.

Results: As of 10 September 2020, 126 patients have been included from five countries/regions: Australia (n=15), Hong Kong (n=2), Korea (n=95), Singapore (n=10) and Taiwan (n=4). Patient characteristics and CFZ utilisation by planned regimen are shown (Table). To date, the regimens prescribed were KRd (63%), Kd (33%) and other CFZ-based regimens (4%), including triplet combinations with cyclophosphamide (n=4) and daratumumab (n=1). Overall, 29% of patients reported a history of hypertension, 9% of cardiac disorders, 8% of diabetes mellitus and 1% of pulmonary embolism, prior to CFZ initiation.

Conclusion: Interim results confirm that the standard dosing schedules for KRd and Kd are well tolerated in real-world practice and suggest a very low rate of discontinuation due to CFZ-related AEs, even in the very late stages of MM. Further prospective data collection of patients in routine practice is ongoing.

	KRd (n=80)	Kd (n=41)	Other CFZ* (n=5)
Patient and disease characteristics			
Median age at CFZ initiation, years (range)	64.0 (39–87)	68.0 (46–85)	65.0 (48–67)
Median time since diagnosis, months (range)	27.8 (0.2–243.4)	46.5 (1.0–219.9)	43.1 (12.0–107.3)
Race, n (%)			
Asian	80 (100.0)	28 (68.3)	5 (100.0)
Caucasian	0 (0.0)	12 (29.3)	0 (0.0)
Other	0 (0.0)	1 (2.4)	(0.0)
ISS stage at MM diagnosis, n (%)			
I	24 (30.0)	6 (14.6)	2 (40.0)
II	18 (22.5)	8 (19.5)	1 (20.0)
III	24 (30.0)	10 (24.4)	2 (40.0)
Unknown or missing	14 (17.5)	17 (41.5)	0 (0.0)
Cytogenetic risk at diagnosis,† n (%)			
High/unfavourable	16 (20.0)	9 (22.0)	2 (40.0)
Intermediate	13 (16.3)	2 (4.9)	0 (0.0)
Normal (favourable)	23 (28.8)	6 (14.6)	0 (0.0)
Unknown/not done or missing	28 (35.0)	24 (58.5)	3 (60.0)
Number of lines of prior treatment, n (%)			
1	51 (63.8)	9 (22.0)	1 (20.0)
2	19 (23.8)	6 (14.6)	0 (0.0)
3	6 (7.5)	8 (19.5)	2 (40.0)
4 or more	3 (3.8)	18 (43.9)	2 (40.0)
Missing	1 (1.3)	0 (0.0)	0 (0.0)
Lenalidomide refractory,‡ n (%)	1 (1.3)	22 (53.7)	2 (40.0)
Bortezomib refractory,‡ n (%)	21 (26.3)	11 (26.8)	2 (40.0)
Patients with prior HSCT, n (%)	44 (55.0)	21 (51.2)	4 (80.0)

	KRd (n=80)	Kd (n=41)	Other CFZ* (n=5)
CFZ administration characteristics			
Carfilzomib dosing schedule, n (%)			
27 mg/m² twice weekly	77 (96.3)	4 (9.8)	0 (0.0)
56 mg/m² twice weekly	0 (0.0)	30 (73.2)	0 (0.0)
Other	3 (5.0)	7 (17.1)	5 (100.0)
Received 20 mg/m² as first dose, n (%)	66 (82.5)	33 (80.5)	4 (80.0)
With CFZ dose reduction, n (%)	21 (26.3)	12 (29.3)	2 (40.0)
Median number of cycles§ (range)	11.0 (1–18)	8.0 (1–25)	8.0 (4–12)
Continuing CFZ treatment, n (%)	54 (67.5)	21 (51.2)	4 (80)
Reason for discontinuing CFZ, n (%)			
Investigator decision	2 (2.5)	0 (0.0)	0 (0.0)
Adverse event	3 (3.8)	2 (4.9)	0 (0.0)
Disease progression/refractory	11 (13.8)	12 (29.3)	1 (20.0)
Patient request	2 (2.5)	3 (7.3)	0 (0.0)
Death	1 (1.3)	1 (2.4)	0 (0.0)
Transplant	1 (1.3)	0 (0.0)	0 (0.0)
Other	6 (7.5)	2 (4.5)	0 (0.0)

*4 patients received KCyd and 1 received Kd-dara. †Cytogenetic risk level is determined by investigator based on medical chart; ‡According to IMWG definition: a subject is classified as refractory to a drug if they meet one of the following three criteria: 1) Best response to any regimen containing the drug is either stable or progressive disease; 2) Reason the drug was stopped is progression with any regimen containing the drug; 3) Date of relapse/progression is (strictly) after the statistical analysis date and within 60 days (inclusive) after the stop date of the drug in any regimen containing the drug; §Total number of treatment cycles in which ≥1 dose of CFZ was administered. CFZ, carfilzomib; HSCT, haematopoietic stem cell transplantation; ISS, International Staging System; Kd, carfilzomib and dexamethasone; Kd-dara, carfilzomib, daratumumab and dexamethasone; KCyd, carfilzomib, cyclophosphamide and dexamethasone; KRd, carfilzomib, lenalidomide and dexamethasone; MM, multiple myeloma.

H140

Survival among older patients (pts) with previously treated multiple myeloma (MM) treated with selinexor, bortezomib, and dexamethasone (XVd) in the BOSTON study

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Aim: MM affects older pts that are vulnerable to treatment related toxicity and have significant morbidity and mortality, requiring dose modifications or suboptimal treatment. We aim to assess efficacy and tolerability of XVd in older compared to younger pts with relapsed MM.

Method: BOSTON is a phase 3, randomized, open-label study of once weekly XVd vs. twice weekly Vd in pts with 1-3 prior regimens. Post-hoc analyses were performed to compare survival in pts ≥65 vs <65.

Results: Pts treated with XVd or Vd who were ≥65 were 109/132 and 86/75 who were <65, respectively.

Median PFS was prolonged with XVd vs. Vd, across age groups: ≥65 (HR, 0.55 [95% CI, 0.37-0.83] P=0.002) and <65, (HR, 0. 74 [95% CI, 0.49-1.11], P=0.07). Vd was associated with lower ORR (64.4%) vs. XVd (76.1%) (OR, 1.77 [95% CI, 1.00-3.11], P=0.024) in pts ≥65. ORR in pts <65 was 76.7% with XVd and 58.7% (OR, 2.33 [95% CI, 1.18-4.59], P=0.007) with Vd. Median OS for the overall population was not reached for both arms (HR=0.86; p=0.193). Median OS was not reached in pts ≥65 with XVd and was 28.6 months with Vd (HR=0.60; 95% CI, 0.38-0.94; p=0.012). There was no difference in OS for pts <65 (HR=1.52; 95% CI, 0.86-2.68; p=0.926). Pts ≥65 had lower incidence of death with XVd vs. Vd (29 vs 56). There were 32 deaths with XVd and 19 with Vd in pts <65.
Grade ≥ 3 TEAEs were not more frequent in older pts. Amongst pts ≥65, PN (any grade) was lower: XVd (32.1%) vs. Vd (46.5%); (OR 0.57 [95% CI 0.34-0.97], p=0.017), including lower incidence of grade ≥3 PN (XVd 4.6% vs. Vd 11.6%). In pts <65, PN (any grade) was 32.6% (XVd) vs. 48.0% (Vd); (OR 0.42 [95% CI 0.21-0.82], p=0.006).
Conclusion: In older pts, XVd was associated with significant survival benefit, improved PFS and OR.

H141

New targets and new approaches in multiple myeloma: extracellular vesicles as functional liquid biomarkers

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Aims: To define the content of circulating small extracellular vesicles (sEV) for the optimization of liquid biopsy in multiple myeloma (MM), and to better understand the role of sEV in regulating the tumor microenvironment and promoting MM progression.

Methods. sEV were isolated from 1mL of peripheral blood plasma (PBPL) using a commercial kit. Proteomic profiling (nLC and high-resolution mass spectrometry, Orbitrap HF-X) of PBPL-sEV derived from 10 healthy donors (HD) and 8 MM, 4 smouldering MM,10 monoclonal gammopathy of undetermined significance (MGUS) patients, and functional studies using a co-culture system with stromal cells HS5 and human MM cell lines (HMCL) were performed.

Results: MM-sEV regulate the tumour microenvironment favouring HMCL proliferation and drug resistance to the proteasome inhibitor bortezomib when HMCL were co-cultured for 24h with HS5 cells pre-treated with MM-sEV compared to untreated HS5 cells or pre-treated with HD-sEV or MGUS-sEV.
A total of 412 proteins were detected and quantified by proteomic profiling of PBPL-sEV with 13 reported as highly enriched in EV marker databases (ExoCarta top 100) and 8/13 corresponding to universal cancer markers as proposed by Hoshino et al (Cell, 2020).
Comparative analysis of sEV between the 4 cohorts revealed 241/412 co-identified proteins. Gene ontology analysis of co-identified proteins (G:Profiler; $p<0.05$) revealed enrichment for cellular component terms such as “extracellular vesicles/exosomes” and for several biological processes including “cell communication”, “endocytosis”, “cell migration”, “cellular response to stimulus”, “immune response”. A specific protein signature identified in MM-sEV (IGHV6-1, SOD1, LPA, VIM, CFHR1) was found in >30% of MM-sEV but <30% HD-sEV.

Conclusions: The characterization and proteomic profiling of disease-specific circulating sEV as a biomarker discovery strategy may provide translational applications in MM. Importantly, MM-sEV may play an important role in disease progression by re-programming the tumour microenvironment.

H142

Evaluation of the lenalidomide patient access program opened for the maintenance treatment of multiple myeloma in patients post stem cell transplantation.

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Aim:

- In Australia, lenalidomide for the maintenance treatment of patients with newly diagnosed multiple myeloma (NDMM) who have undergone autologous stem cell transplantation (ASCT) was TGA approved in February 2018 and PBS listed April 2020.
- In November 2019 Celgene Australia, a Bristol Myers Squibb company, opened a Patient Access Program (PAP), providing lenalidomide free of charge to patient's whose treating physician deemed it an appropriate treatment.
- In NDMM, following response to primary therapy, maintenance treatment may delay progression and prolong overall survival; however, maintenance is not an established treatment option in Australia. Lenalidomide is the only approved agent, and only post-ASCT.
- This review analysed the impact, uptake & utilisation of the PAP.

Method: This was a retrospective review of PAP enrolment data from the CEL medical operations database.

Results:

- The lenalidomide PAP was open for 4.5 months (15th November 2019 to 31st March 2020), and enrolled a total of 366 patients from 83 unique participating institutions and 163 unique participating prescribers.
- Uptake of the PAP was fast with 44% (n = 161) of the total patients enrolled within the first 6 weeks.
- Inclusion in the PAP was independent of location. Geographical data showed all states were represented & uptake largely aligned with patient demographic data. (Table 1).

Table 1: Patient Enrolment by State

	Patient Numbers (n=366)	Relative %
NT	3	0.8%
ACT	6	1.6%
TAS	7	1.9%
SA	45	12.3%
WA	48	13.1%
QLD	68	18.6%
NSW	91	24.9%
VIC	98	26.8%

Conclusion: Demand for the PAP was widespread across the haematology community with a diversity of prescribers and institutions participating. This, coupled with the speed of uptake, demonstrated the high unmet medical need for this patient population. The PAP set up post TGA registration, reduced the time to affordable access for patients ahead of reimbursement.

Daratumumab, bortezomib, dexamethasone (D-Vd) versus bortezomib and dexamethasone (Vd) in relapsed or refractory (RR) multiple myeloma (MM): pooled subgroup analysis of LEPUS and CASTOR

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Aim: In phase 3 CASTOR and LEPUS studies, addition of daratumumab to standard-of-care demonstrated significantly improved progression-free survival (PFS) and depth of response in patients with newly diagnosed MM or RRMM. A pooled analysis of LEPUS (Chinese patients) and CASTOR (global patients) examined efficacy of D-Vd vs Vd based on age, cytogenetic risk status, and renal function (median follow-up, 7.5 months).

Method: Eligible patients, who received ≥1 prior line of therapy, were randomly assigned (LEPUS, 2:1; CASTOR, 1:1) to receive eight 21-day cycles of Vd ± D. Primary endpoint: PFS.

Results: Overall, 211 (D-Vd, 141 vs Vd, 70) patients in LEPUS (median age [range], 61 [28-82] years) and 498 (251 vs 247) in CASTOR (64 [30-88] years) were included. Baseline characteristics were similar between LEPUS and CASTOR and balanced between treatment arms, except for median body weight (LEPUS: 67 kg; CASTOR: 76 kg). Treatment with D-Vd vs Vd demonstrated a consistent PFS benefit across age, cytogenetic risk status, and renal function subgroups (Table). Treatment with D-Vd vs Vd led to longer median time to progression and duration of response in all subgroups; rates of overall response, very good partial response or better, and complete response or better also improved. The most common grade 3/4 treatment-emergent adverse events (TEAEs; D-Vd/Vd) included thrombocytopenia (LEPUS, 51%/37%; CASTOR, 45%/33%), lymphopenia (44%/29%; 10%/3%), neutropenia (16%/6%; 13%/4%), and hypertension (12%/3%; 7%/1%); rates of serious TEAEs (49%/38%; 42%/34%) and TEAEs leading to treatment discontinuation (4%/3%; 7%/9%) or death (4%/10%; 5%/6%) were consistent. Rates of infusion-related reactions with D-Vd (mostly grade 1/2 and occurring during the first infusion) were similar between LEPUS (38%) and CASTOR (45%).

Table: Median PFS with D-Vd and Vd in Patients Pooled from LEPUS and CASTOR[a]

	Median PFS, months (n)		HR (95% CI)	*P* value
	D-Vd	Vd		
Age, years				
< 65	NR (224)	6.6 (166)	0.35 (0.24-0.50)	<0.00001
65-74	NR (138)	6.2 (109)	0.35 (0.22-0.54)	<0.00001
≥ 75	NR (30)	8.1 (42)	0.32 (0. 10-0.98)	0.03521
Cytogenetic risk status[b]				
Standard risk	NR (232)	6.3 (178)	0.30 (0.21-0.42)	<0.00001
High risk	11.1 (87)	6.5 (64)	0.39 (0.21-0 71)	0.00160
Renal function				
CrCl ≤ 60 ml/min	NR (98)	6.3 (88)	0.47 (0.28-0 76)	0.00200
CrCl > 60ml/min	NR (286)	6.6 (215)	0.29 (0.21-0.40)	<0.00001

HR, hazard ratio; NR, not reached; CrCl, creatinine clearance. [a]Intent-to-treat population; median follow up, 8.2 months (LEPUS) and 7.4 months (CASTOR). [b]As evaluated by local fluorescence in situ hybridization or karyotyping; high risk was defined as the presence of t(4;14), t(14;16)or dell7p abnormalities.

Conclusion: D-Vd significantly improved PFS in Chinese and global patients with RRMM who received ≥1 prior therapy, regardless of age, cytogenetic risk status, or renal function. No new safety concerns were identified.

Early pharmacodynamic changes in T-cell activation, proliferation, and cytokine production in patients with relapsed/refractory multiple myeloma (RRMM) treated with cevostamab (anti-FcRH5xCD3)

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Aim: To report preliminary pharmacodynamic (PD) biomarker data from the ongoing Phase-I dose-escalation study (NCT03275103) of cevostamb (anti-FcRH5xCD3) monotherapy in patients with RRMM.

Method: Patients received IV cevostomab in 21-day-cycles. Risk of cytokine release syndrome (CRS) was mitigated by giving single step dose (0.05–3.6mg) in Cycle (C) 1 Day (D) 1; target dose (0.15–132mg) given on C1D8 and D1 of each subsequent cycle. Whole blood flow cytometry, plasma cytokine electrochemiluminescence and digital ELISA were used to assess PD changes in peripheral blood (PB). Bone marrow (BM) biopsy dual CD138/CD8 immunohistochemistry staining and BM aspirate flow cytometry were used to assess tumour biomarkers at baseline and pre-C2.

Results: All 51 patients were biomarker evaluable at cut-off, with detectable FcRH5 expression on myeloma cells. PD changes in PB were dose-dependent and were detected within 24–192 hrs post-C1D1 infusion. Transient reduction in circulating T-cells was detected 24 hrs after the 0.3–1.8mg C1D1 with recovery by C1D8. T-cell activation and elevation of IFN-γ in plasma was detected 24hrs post-infusion, while T-cell proliferation peaked by C1D8. At the 3.6mg C1D1 dose, CD8 T-cell activation and proliferation were up to 20-fold higher than at baseline. IL-6 elevation was detected at C1D1 and C1D8 post-infusion; with elevation higher at D1 than D8. Peak IL-6 levels were associated with CRS severity on C1D1 (3.6mg step dose) but not on C1D8 (20–132mg target dose); suggesting that step-up dosing mitigated the risk of severe CRS. On-treatment increases in CD8+ tumour-infiltrating T-cells (TILs) were higher among responders at the end of C1.

Conclusion: Results confirm the mechanism of action of cevostomab and support C1 step-up dosing for CRS mitigation in RRMM. Early data suggest that higher peripheral CD8 T-cell expansion and TILs were detected, at the end of C1, in responders than in non-responders.

H145

Peripheral blood stem cell (PBSC) mobilisation following VRd induction: Real-world single-centre experience

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Aim: (a) Explore if VRd (Bortezomib-Lenalidomide-dexamethasone) induction impacts on PBSC mobilisation compared to VCd (Bortezomib-Cyclophosphamide-dexamethasone); (b) Evaluate the optimal method of PBSC mobilisation following VRd by comparing efficacy of G-CSF vs G-CSF and cyclophosphamide.

Method: We compared three cohorts who had PBSC mobilisation between January 2019 to March 2021 at St Vincent's Hospital Melbourne: (1)VCdx4 with G-CSF; (2)VRdx4 with G-CSF and cyclophosphamide; (3)VRdx3 with G-CSF. Data collected included number of apheresis, total CD34 yield and reasons for failure or recollections.

Results: 56 patients were identified (median age 60 years, range 33-70). Target CD34 was defined as minimum of 2 or 4x10^6/kg for planned single or tandem autologous stem cell transplants (ASCT) respectively. Results obtained are summarised below:

	(1)-VCdx4; G-CSF	**(2)-VRdx4; G-CSF+cyclo**	**(3)-VRdx3; G-CSF**	**p-value (1)vs(3)**	**p-value (2)vs(3)**
n	23	20	13		
Median days from chemotherapy(IQR)	34.5 (31-42)	49.5 (40-60.8)	41.5 (36-50)	0.04	0.08
Median no. of apheresis(range)	2 (1-5)	2 (1-4)	2 (1-3)		
Mean no. of apheresis(95%CI)	2.52 (2.18-2.86)	1.85 (1.50-2.20)	2.17 (1.71-2.62)	0.20	0.25
Mean total CD34 (10^6/kg;95%CI)	6.27 (4.52-8.01)	8.89 (7.02-10.75)	5.96 (4.15-7.76)	0.78	0.036
Recollection/failures	3/0	1/0	0/1		
Proportion of patients with yields≥2x10^6/kg	23/23 (100%)	20/20 (100%)	12/13 (92%)		
Proportion of patients with yields≥4x10^6/kg	15/23 (65%)	19/20 (95%)	8/13 (61%)		

Reasons for failure or recollection were poor disease response (n=3) or cytopenias (n=3). Of all the VRd patients, only one had poor collection despite G-CSF, cyclophosphamide and plerixafor. Only 4/13 patients who had VRd with G-CSF alone had yields of <4x10^6/kg; all were planned for one ASCT only.

Conclusion: Successful PBSC mobilisation is possible after three cycles of VRd with G-CSF alone. There is significantly improved PBSC yield and a trend towards reduced apheresis days with addition of cyclophosphamide. However overall success rates as defined by achieving target yield is comparable to the G-CSF only cohort.

H146

Significant bortezomib dose reduction is seen with twice-weekly bortezomib, lenalidomide and dexamethasone (VRd) induction in transplant-eligible multiple myeloma (MM) patients: Real-world single-centre experience

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Title: Significant bortezomib dose reduction is seen with twice-weekly bortezomib, lenalidomide and dexamethasone (VRd) induction in transplant-eligible multiple myeloma (MM) patients: Real-world single-centre experience

Aim: Dosing schedule of VRd induction in MM is inconsistent amongst Australian institutions. We evaluated the tolerability of VRd and dose reduction (DR) incidence for transplant-eligible patients.

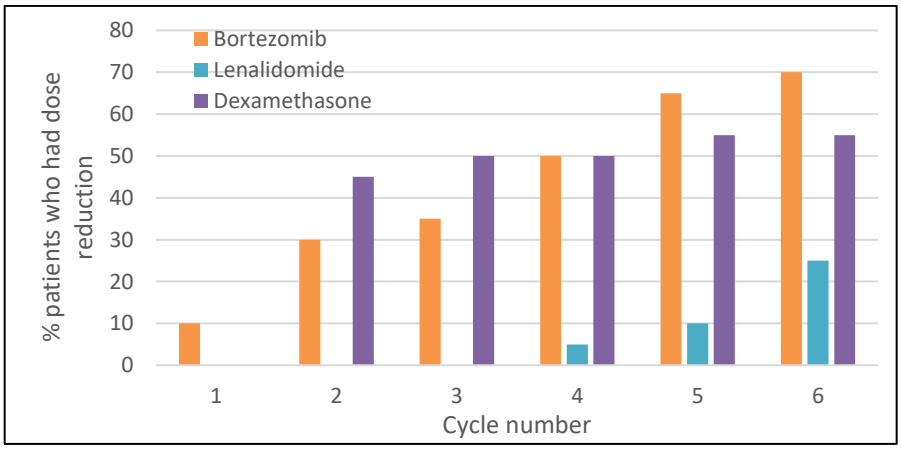
Method: We identified 25 patients who had VRd up until March 2021 at St Vincent's Hospital Melbourne. Data collected include number of cycles, dosages, adverse events and disease response.

Results: 20 patients started with twice-weekly bortezomib 1.3mg/m2 (Days1,4,8,11), lenalidomide 25mg Days1-21 and dexamethasone 40mg weekly, every 28-days, for six cycles. Five patients had weekly bortezomib 1.3mg/m2 (Days1,8,15,22), with the same Rd dose, every 28-days, for 3-5 cycles.

Amongst the twice-weekly cohort, proportion of patients requiring bortezomib DR was 10% in cycle-1, 30% in cycle-2, 35% in cycle-3, 50% in cycle-4, 65% in cycle-5 and 70% by cycle-6, for peripheral neuropathy. Only 5% required lenalidomide DR by cycle-4 and 25% by cycle-6 for cytopenias. 45% of patients required dexamethasone DR by cycle-2 and 55% by cycle-6 for mental agitation or insomnia. Graph 1 summarises this. 2/20 patients tolerated full dose triplet-therapy throughout six cycles; both were young (<40years). Mean total dose delivered as a percentage of intended total dose over six cycles was 68% for bortezomib (95%CI 57-80%), 94% for lenalidomide (88-100%) and 71% for dexamethasone (59-82%). 1/20 patient was primary refractory; the rest had durable responses (≥VGPR) post ASCT and are all in maintenance phase.

Amongst the five patients on weekly bortezomib schedule, all tolerated full dose bortezomib and lenalidomide for 3-5 cycles, with only one requiring dexamethasone DR by cycle-2. VGPR (n=2) or PR (n=3) was achieved post-induction.

Conclusion: With the twice-weekly VRd induction schedule, bortezomib and dexamethasone DR was frequent in our experience, supporting the move towards a weekly 28-day schedule, particularly for non-aggressive MM.



Graph 1: Proportion of MM patients requiring dose reductions per cycle in a twice-weekly VRd schedule

H147

Single institution experience and management recommendations in supportive care for patients with relapsed/refractory multiple myeloma (RRMM) receiving selinexor.

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Aim: Selinexor is a first-in-class XPO inhibitor used in treatment of RRMM. Australian experience is limited. We aim to explore its pattern of use and tolerability in the real world setting within a single institution.

Method: We identified eight patients treated with selinexor between July 2018 to March 2021 at St Vincent's Hospital Melbourne. Data collected included dosage, number of cycles, adverse events (AE) and supportive management implemented.

Results: Patients were heavily pre-treated (median prior lines of therapy of 6, range 1-9). Patients had doublet therapy with selinexor and dexamethasone (Xd) (n=1) or triplet therapy with Xd plus velcade (n=2) or izaxomib (n=4) or belantamab (n=1). Median total number of cycles was 2.5 (range <1-9). Six patients were commenced on 100mg weekly dose. One had multiple comorbidities and was commenced on a lower dose of 80mg upfront. All patients experienced at least one AE with six patients requiring early dose reduction or drug holiday during cycle 1-2. AE included gastrointestinal (n=5), constitutional symptoms of anorexia or fatigue (n=3), thrombocytopenia (n=5) and hyponatraemia (n=2). Vigilant monitoring and early management of AE was undertaken including elective 48-hour admissions on commencement, prophylactic anti-emetics, early olanzapine use, G-CSF, platelet transfusions and weekly reviews in cycle one. Causes of discontinuation were disease progression (n=5) or intolerable AE (n=3). Only one patient achieved complete remission but ceased after cycle 9 due to gastrointestinal symptoms.

Conclusion: AE with selinexor use is predictable and can be tolerated with timely dose reductions, prophylactic treatment and early supportive care. It is anticipated that movement of selinexor into earlier lines of therapy will result in improved tolerance given that these patients have less cumulative toxicities, better functional status and superior bone marrow reserve. A detailed summary of toxicity management in two patient cases will be presented at the meeting for education.

Interim results of a time and motion survey regarding subcutaneous vs intravenous administration of daratumumab in patients with relapsed or refractory multiple myeloma

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Aim: Intravenous daratumumab takes several hours while subcutaneous daratumumab takes ≈5 minutes to administer. Results from phase 3 COLUMBA (NCT03277105) supported the approval of subcutaneous daratumumab for multiple myeloma in the US and Europe. A time and motion survey assessed healthcare professionals' (HCPs) understanding of workflow and time estimates (beyond injection time alone) for daratumumab SC vs IV in patients with relapsed/refractory multiple myeloma. The results are reported.

Method: A web-based, prospective survey, conducted at COLUMBA sites that actively enrolled patients, collected data from HCPs. The primary endpoints: mean and median HCP active time for prespecified activities (drug preparation, drug administration/patient care). A post hoc analysis estimated patient chair time.

Results: Twenty-six respondents from 8 countries completed the survey. For the first dose, median total HCP active time reduced by 66.5% with daratumumab SC (98.7 minutes [22.6 minutes for drug preparation + 76.0 minutes for drug administration/patient care]) vs IV (294.2 minutes [30+264.2 minutes]); for subsequent doses, reduction was 57.8% (SC, 82.2 [22.6+59.6] minutes; IV, 194.9 [30+164.9] minutes). For both SC and IV dosing, the proportion of HCP active time on drug preparation or administration/patient care were similar between first and subsequent administrations. Extrapolated for Years 1 (23 doses) and 2 (13 doses), the estimated HCP active time/patient was considerably lower for SC (31.8 and 17.8 hours, respectively) vs IV (76.4 and 42.2 hours) dosing. Estimated chair time for the first and subsequent doses was also considerably lower for SC (8.6 and 6.9 minutes, respectively) vs IV (445.6 and 243.1 minutes) dosing. Results were confirmed by a sensitivity analysis using fully validated data from 13 patients.

Conclusion: Daratumumab SC vs IV is associated with less HCP active time on prespecified activities. This may benefit patients (less time away from home, family, work) and increase HCPs' efficiency (treat more patients)

H150

Chromosome 1 Abnormalities in Multiple Myeloma

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Aim: Our aim was to report clinical features and outcomes of multiple myeloma (MM) patients with chromosome 1 abnormalities (C1A) detected by FISH, gain of 1q and/or deletion of 1p, treated in the era of novel agents.

Method: Patients diagnosed with MM between August 2016 and December 2019 at two tertiary institutions in Western Australia were included.

Results: Of 112 patients 37% (n=41) had C1A and 63% (n=71) had No C1A. Of patients with C1A 12% (n=5) had deletion 1p, 73% (n=30) gain 1q, and 15% (n=6) had both del1p and gain1q.

Patients with C1A were more likely to present with anaemia (54% C1A vs 33% No C1A, p=0.04) and have IgA protein subtype (49% C1A vs 14% No C1A, p=0.005). High risk cytogenetic abnormalities (HRA) were more common in C1A cohort (37% C1A vs 14% No C1A, p=0.009).

Frontline therapy was most commonly bortezomib based (83% for C1A and 70% for No C1A) followed by lenalidomide based regimens (10% C1A vs 23% No C1A) with similar upfront transplant rates (38% C1A vs 43% No C1A, p=0.69). Overall response rate (ORR) to frontline therapy was 89% for C1A and 85% for No C1A, p=0.43.

Median progression free survival (PFS) and overall survival (OS) were similar between cohorts (median PFS 14 months C1A vs 21 months No C1A, p=0.11; median OS 35 months C1A vs Not reached No C1A, p=0.25). Patients with C1A with concurrent HRA had the worst prognosis (median PFS 8 months C1A+HRA vs 25 months C1A only, p=0.06; median OS 12months C1A+HRA vs Not reached C1A only, p=0.0006).
Conclusion: Our data suggest that the poor prognosis in C1A patients may be driven by higher rates of HRA with patients having C1A and HRA having a dismal prognosis. This cohort of patients may benefit from intensification of upfront therapy and this requires further study.

Variable	C1A n=41	No C1A n=71	P value
Age, median years (range)	68 (45-90)	67 (44-91)	0.91
Male	19 (46)	43 (61)	0.17
Hb <100	21 (54)	23 (33)	0.04
BMPCs, median IQR	50 (25-70)	50 (25-75)	0.95
Renal impairment	5 (13)	13 (19)	0.59
Lytic lesions	31 (77)	45 (65)	0.2
ISS stage n=93			0.71
I	10 (33)	22 (35)	
II	9 (30)	23 (37)	
III	11 (37)	18 (29)	
High risk cytogenetics	15 (37)	10 (14)	0.009

H151

Utility of aspirate, trephine and flow cytometry in plasma cell enumeration for plasma cell dyscrasias

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Aim: Accurate quantification of plasma cells in bone marrow is essential in diagnosing and prognosticating plasma cell disorders. We compare enumeration of plasma cells by aspirate, trephine and flow cytometry and examine the utility of immunophenotype in diagnostic bone marrows for myeloma.

Method: We retrospectively analyzed 71 consecutive bone marrow aspirate and trephine samples in patients with suspected myeloma at our tertiary institution. Plasma cells were quantified by a 300-cell differential count on aspirate slides, examination of trephine section, and flow cytometric analysis using CD138 and CD38 gating criteria. Aberrant immunophenotype was defined as CD56 positivity and CD19 negativity.

Results: Baseline characteristics are listed in Table 1. 72% of patients had a suspected plasma cell disorder while 28% were being restaged following therapy for multiple myeloma.

Median difference in plasma cell percentage between paired trephine and aspirate samples was 5% (0–73). 36.8% (14/38) of patients had <10% of plasma cells on aspirate, but a diagnosis of myeloma on trephine. 43.6% (31/71) of trephine samples were analyzed using CD138 and MUM1 immunohistochemistry. The median plasma cell percentage by this was 30%, relative to 15% in samples examining morphology alone.

Flow cytometry underestimated plasma cell involvement compared with aspirate and trephine samples. Median difference between aspirate and flow cytometry was 4% (0-48) and between trephine and flow cytometry 45% (0–86). Aberrant immunophenotype was present in 92.1% with myeloma, 60% with MGUS, 62.5% with lymphoproliferative disorders, 50% in remission and 100% with normal marrows.

Conclusion: Bone marrow aspirate alone missed 37% of myeloma diagnoses. Flow cytometry greatly underestimates plasma cell percentage. The detection of aberrant immunophenotype failed to assist in differentiating plasma cells dyscrasias. Trephine immunohistochemistry is reliable and should be routinely used for accurate prediction of plasma cell count.

Table 1: Baseline characteristics

Variable	Baseline characteristics
Age, median (range), years	69.5 (46-96)
Paraprotein, median (range), g/L	7 (0-57)
IgG (%) IgM (%) IgA (%)	49.3 7 7
IMWG Criteria for Multiple Myeloma (%)	53.5
IMWG Criteria for MGUS (%)	14
Lymphoproliferative disorder (%)	11
Normal or remission (%)	17
Aspirate, median (range), %	5.5 (0-90
Trephine, median (range), %	17.5 (0-9)
Flow cytometry, median (range), %	1.0 (0.1-12)

H152

Incidence of AL amyloidosis in diagnostic bone marrow biopsies and association with concurrent systemic amyloidosis in patients with newly diagnosed multiple myeloma: A series of 231 cases

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Aim(s): To determine the incidence of bone marrow (BM) amyloidosis in patients with newly diagnosed multiple myeloma (MM) and to correlate the presence of BM amyloidosis with concurrent systemic amyloidosis.

Method: Consecutive patients with newly diagnosed MM who underwent a diagnostic BM biopsy at the Alfred Hospital were identified for this retrospective study (2007-2020). Congo Red stains (CRd) were performed on trephines and were evaluated by transmission birefringence microscopy. Historic trephine samples with no CRd performed were stained and examined by two independent examiners for positivity, defined as focal (limited to blood vessel) or diffuse. All clinical details were collected from the electronic medical record.

Results: Of 248 identified patients, 231 had CRd data available (17 samples were not able to be retrieved). 7/231 (3%) patients had positive CRd: 6 focal, 1 diffuse. Of these 7 patients, 2 had known AL amyloidosis (1 hepatic, 1 renal) at the time of BM biopsy.

22 patients had known or suspected symptomatic AL amyloidosis: 20 had biopsy-proven organ amyloidosis at the time of BM biopsy, 2 had cardiac amyloidosis later identified on autopsy. BM CRd was negative for 20/22 (91%) patients.

The positive predictive value for BM CRd predicting systemic AL amyloidosis was 28.6%, the negative predictive value was 91%.

Conclusion: In our cohort, the incidence of BM trephine CRd positivity was low and poorly sensitive for predicting concurrent systemic AL amyloidosis. A negative CRd on BM does not abrogate the need for careful amyloid-specific review at the time of diagnosis. Previous studies have reported a 25-40% incidence of amyloid on BM biopsies, however were on smears rather than trephine[1,2]. Our study is the largest to date to evaluate the incidence of trephine CRd status and its correlation with systemic amyloidosis in newly diagnosed MM patients and is consistent with previously reported studies[3].

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H153

Single centre experience of tandem autologous stem cell transplantation in multiple myeloma.

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Aim: Available data suggests a benefit for tandem autologous stem cell transplantation (TASCT) in patients with high risk (HR) multiple myeloma (MM).[1,2,3] In many jurisdictions outside of Europe, TASCT is not routinely performed due to toxicity concerns and patient refusal to proceed to a second autograft. We set out to assess the feasibility, tolerability, resource utilisation and patient reported experience of TASCT at our centre.
Method: We performed a retrospective analysis of all patients undergoing TASCT at our centre between September 2017 and February 2021. Patients were defined as HR according to IMWG criteria or if they had a sub-optimal response (< PR) to bortezomib-based induction therapy. Patient demographics, disease characteristics as well as surrogate markers of toxicity such as length of hospital stay, time to second transplant, engraftment kinetics following the first and second autograft, ICU admission, sepsis, parenteral nutrition and opioid use were obtained from patient medical records.
Results: During the review period, 18 patients with MM (n=17) and primary plasma cell leukaemia (n=1) underwent TASCT. The mean age at first transplant was 61.3 years (41 – 72 years). The mean length of hospital stay was significantly longer during the 1st transplant compared to the 2nd (18.5 vs 16.6 days, p=0.037). No patients required ICU admission and there were no transplant-related deaths. There was a trend towards greater parenteral nutrition use during the 1st transplant (44% vs 40%) with parental opioid use more likely with the second transplant (39% vs 50%). Neutropenic sepsis was observed more frequently following the 1st transplant (100% vs 89%), and positive blood cultures more common during the 2nd transplant (44% vs 81%).
Conclusion: Based on this small retrospective analysis, TASCT is feasible, tolerable and safe. Additional data on engraftment and patient experience will also be presented.

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H154

Initial results of the ALIGN study - the effects of AmyLoIdosis on the GastroiNtestinal tract in an Australian population

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Aim: Gastrointestinal (GI) symptoms, such as loss of appetite and weight, are common in patients with light chain (AL) or transthyretin (ATTR) amyloidosis, however, there is little published data on the precise mechanism of these symptoms, and optimal therapy (1). We designed a study in patients with amyloidosis ("ALIGN") to better understand the incidence, causes and treatment patterns of GI symptoms.

Method: A single centre observational study of individuals with a new diagnosis of systemic or localised amyloidosis with gastrointestinal symptoms or biopsy proven gastrointestinal involvement. Participants are recruited from the Victorian and Tasmanian Amyloidosis Service at Eastern Health. During the study, patients are observed using clinical, biochemical and imaging parameters, including liver ultrasonography, gastric emptying studies and Fibroscans for a period of 2 years.

Results: Between October 2019 and March 2021, 7 patients have been recruited.

Table 3: Patients' Characteristics and Demographics

Characteristic	**Value**
Number of patients; n.	7
Age at recruitment; median (range)	80 (65, 88)
Sex; n. (%)	Male: 6 (85.7%) Female: 1 (14.3%)
Amyloidosis Type; n. (%)	Immunoglobulin Light Chain (AL) Amyloidosis: 2 (28.6%) Transthyretin Related (TTR) Amyloidosis: 5 (71.4%)

Majority of the patients were diagnosed with TTR amyloidosis followed by AL amyloidosis (Table 1). Almost half of the patients (42.9%) had GI symptoms at baseline, including bloating, anorexia, xerostomia, diarrhoea and weight loss. One patient had incidental biopsy proven gastrointestinal involvement of the terminal ileum.

Among the 5 patients with baseline FibroScan results, 80% have abnormal readings of above 7kPa which suggests a degree of fibrosis present(2). Of the 5 patients who underwent gastric emptying studies, 1 (20%) was diagnosed with gastroparesis.

Conclusion: Gastrointestinal symptoms are common in amyloidosis patients at diagnosis. FibroScan results suggest a high incidence of hepatic fibrosis. Results from other parameters may reveal important patterns as recruitment and follow-up of patients are ongoing.

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H155

Tandem autologous + non-myeloablative allogeneic-SCT in relapsed multiple myeloma: a joint report from the Alfred and Myeloma and Related Diseases Registry (MRDR)

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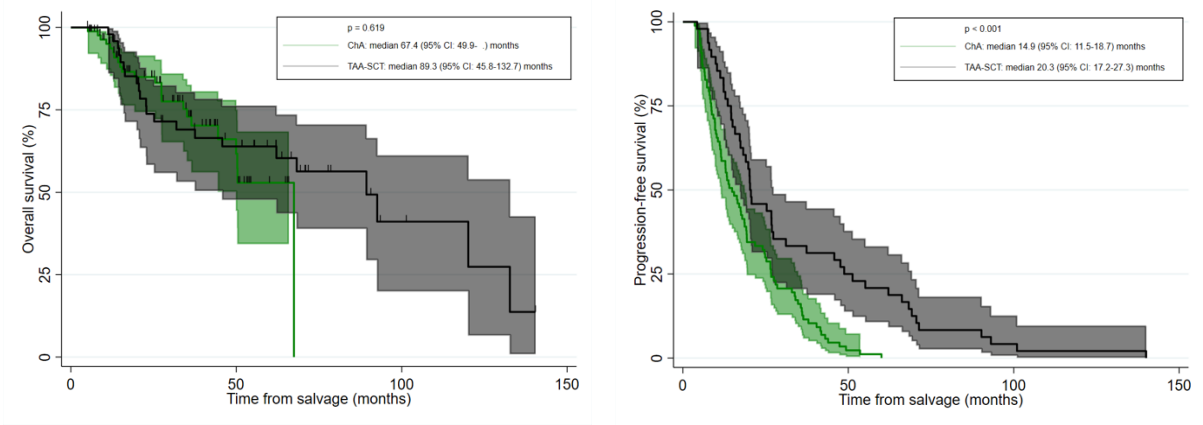
Aim: Graft-versus-myeloma (GvM) effect from allogeneic-SCT potentially affords long-term disease control in multiple myeloma (MM). A salvage program incorporating chemotherapy followed by tandem autologous + non-myeloablative allogeneic-SCT (TAA-SCT) may offer a survival advantage over chemotherapy alone (ChA).

Method: Consecutive patients with relapsed MM (R-MM) salvaged with chemotherapy followed by TAA-SCT at the Alfred between Jan-08 and Dec-19 were identified. A 2:1 comparator cohort salvaged with ChA (iMiD agent/PI available) matched for age/sex/ISS-stage, was extracted from the Myeloma and Related Diseases Registry (MRDR)**.** All patients received autologous-SCT as part of their upfront treatment. Survival was assessed by Kaplan-Meier method and compared using log-rank test. Prognostic variables were adjusted using Cox-regression.

Results: 48 patients received TAA-SCT following salvage chemotherapy during the study period; 35% met criteria for high-risk myeloma at diagnosis (ISS-III and/or adverse CG/FISH) with a median age at salvage of 57 [range: 32-68] and 2 prior therapy lines [range: 1-7]. Preceding TAA-SCT, salvage chemotherapy yielded ≥ PR in ~95% of cases; iMiD® and/or PI were used in ~85%. 87 matched patients were identified from the MRDR as the ChA cohort. Baseline characteristics were comparable, except that the TAA-SCT cohort was more heavily pre-treated ($p < 0.001$). With a median follow-up of 51 months, the estimated 5-year OS were similar (**Figure 1)**: TAA-SCT 64% (95%CI: 48%-76%) vs. ChA 53% (95%CI: 34%-68%). However, after adjusting for number of prior therapy lines, an OS advantage was observed in the TAA-SCT relative to the ChA cohort (HR 0.36, 95% CI:0.14-0.91, $p = 0.01$). In addition, PFS was also improved in the TAA-SCT cohort (**Figure 1**, $p < 0.001$), with a 5-year PFS of 21% (95%CI: 11%-33%) vs. 1% (95%CI: 0-6%) for the ChA cohort.

Conclusion: In the iMiD® and PI era, TAA-SCT following chemotherapy remains an effective salvage strategy in selected patients with R-MM, providing an immunological platform for a GvM effect with OS and PFS advantage over chemotherapy alone.

Figure 1. Comparative OS (Left) and PFS (Right) of the TAA-SCT vs. MRDR ChA cohort



H156

Amyloidosis of the respiratory tract : Looks like cancer, but usually doesn't need treatment

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Aim: Localised respiratory tract amyloidosis (LRTA) often presents with symptoms and imaging suggestive of malignancy. LRTA can be laryngeal, tracheobronchial, parenchymal, mediastinal or pleural.[1-3] Symptoms present according to the anatomical region including dyspnoea, haemoptysis, cough and dysphonia.[1-3] There is usually no associated clonal population.[2] We aimed to examine local experience of LRTA at the Victorian and Tasmanian Amyloidosis Service (VTAS) to confirm reports that LRTA is benign with an excellent prognosis that does not require systemic treatment.

Method: We identified LRTA patients from the VTAS database, 2014-2020, Details of patient demographics, treatments, and survival were collected. This study received ethics approval from the Eastern Health Ethics Committee.

Results: We identified 9 patients with LRTA: four cases of laryngeal and five pulmonary/bronchial amyloidosis. Seven patients had the AL subtype and two had an unclear subtype. No patient had extra-respiratory disease. Median follow-up was 36 months (range 24 to 48 months). Median age was 42 (range 24 to 68 years).Patients with laryngeal LRTA presented with hoarse voice that improved after laryngoscopic excision of amyloid nodules. Hoarse voice returned in one patient, who received six months of doxycycline 100mg BD as an anti-fibrillogenic agent with no success. Of the bronchopulmonary patients, two presented with chronic cough, two with haemoptysis and one with incidental pulmonary nodules on chest X-ray. Two patients received doxycycline - one had resolution of haemoptysis while the other patient stabilised after pre-emptive IV immunoglobulin to prevent infective complications. Three maintained clinical quiescence and radiological stability without treatment. No patient died or had systemic disease spread.

Conclusion: Our experience with LRTA is similar to previous reports that suggest an excellent prognosis. Observation and local excision for refractory symptoms are treatments of choice. Doxycycline as an anti-fibrillogenic agent may improve symptoms or help stabilise the growth of deposits from recurrent infections.[4]

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H157

Hemophagocytic lymphohistiocytosis in a patient following AstraZeneca COVID-19 vaccination

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Aim: To describe a case of hemophagocytic lymphohistiocytosis developing 13 days after vaccination with AstraZeneca COVID-19.

Method: DB is a 68 year old man who developed fevers, malaise and lethargy 13 days after receiving his first AstraZeneca COVID-19 vaccination. He had an elevated ferritin of > 10,000ug/L, hypertriglyceridemia, evidence of hemophagocytosis on his bone marrow biopsy, splenomegaly and fevers of > 38.3C. He also developed HIT ELISA positivity, thrombocytopenia and a D-dimer > 10 mg/L in the absence of thrombosis.

Results: DB was managed with no specific interventions except broad spectrum antibiotic cover when he was febrile. His thrombocytopenia recovered, fevers resolved, and D-dimer and ferritin was downtrending. No bacterial, viral or malignant precipitant was found.

Conclusion: This case illustrates that the pro-inflammatory effect of the AstraZeneca COVID-19 vaccination can manifest as a hemophagocytic lymphohistiocytosis syndrome, and the success of expectant management in this condition.

H158

Extramedullary haematopoiesis in a thalassemia patient carrying a complex rearrangement in the beta globin locus

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Aim:
- To highlight the risks of severe extramedullary haematopoiesis (EMH) in NTDT patients and provide an approach to management.
- To emphasise the diagnostic challenges involved in next generation globin gene sequencing and the importance of correlation with phenotype and screening investigations.

Case Presentation: We present the case of a 35-year-old Pakistani male with NTDT who was referred with back pain, ataxia, and radiological evidence of extensive EMH with thoracic cord compression. The patient was acutely managed with steroids, hydroxyurea, and radiotherapy. He was subsequently commenced on a regular transfusion program with iron chelation. A month later, he re-presented with shortness of breath and bilateral pleural effusions. Following extensive investigation, pleural EMH was detected and he underwent bilateral pleurodesis.

Investigations: On initial presentation, the patient had a haemoglobin of 84g/L (MCV 87.3fL). High performance liquid chromatography (HPLC) revealed absent HbA, 98.5% HbF, 1.4% HbA_2 and no abnormal bands. Multiplex ligation-dependent probe amplification demonstrated the common 3.7kb rightward deletion in the alpha globin locus. The beta globin locus appeared heterozygous for a large deletion spanning the delta and beta globin genes. The results were inconsistent with a thalassaemia trait given HbA was absent on HPLC. Detailed investigation on the beta globin locus suggested a 7.4kb delta-beta deletion overlapping an Indian 619bp deletion *in trans*.

Conclusion: EMH is a rare and potentially disabling complication in NTDT patients. The development of EMH can be minimised by the timely institution of therapy including regular red cell transfusion, and accurate molecular diagnosis is crucial in identifying at risk patients. Globin gene loci are complex and often require sequential molecular assays. A detailed clinical history and accurate interpretation of laboratory tests can be critical to the institution of life-saving therapy.

Changes in peripheral leukocyte light scatter parameters with Clostridioides difficile infection

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Aim: Prior studies have shown changes in lymphocytes[1] and monocytes[2] in *Clostridioides difficile* infections. This study aimed to determine the effect of *C. difficile* diarrhoea on leukocyte light scatter characteristics in the Beckmann Coulter DXH800 cell counter.

Method: Retrospective comparison was undertaken on patients with full blood counts (FBCs) concurrently with same-day *C. difficile* stool studies. De-identified FBCs were divided into four groups dependent upon the results of the *C. difficile* stool analysis: active CDI (CDI+, n=17), probable CDI (n=20), non-toxigenic *C. difficile* colonisation (CDI-, n=13) and C. difficile Absent (n=458). Leukocyte cell population data (CPD), including volume, conductivity and five-angle light scattering parameters (LSPs) were compared between CDI+ and Absent groups by Mann-Whitney's U-test. Kruskal-Wallis test was used for CPD multivariate analyses between four groups.

Results: Absolute neutrophil counts were elevated in CDI+ samples compared to CDI- ($P = 0.002$) and *C. difficile* Absent ($P = 0.03$) groups. Lymphocyte low angle light scatter ($P = 0.0003$) and axial light loss ($P = 0.0006$) were both significantly decreased in CDI+ group compared to the other three groups. This suggests a reduced proportion of large granular lymphocytes rather than an increase, as shown previously.[1] Monocyte light scatter parameters were also not associated with active *C. difficile* infection as previously reported,[2] possibly due to change sin the innate immune response as infection progresses.

Conclusion: In this study active *C. difficile* infection was associated with changes in leukocyte cell population data, implying a change in the innate immune response. These findings show heterogeneity compared with previous reports and the parameters are therefore unreliable predictors of CDI in symptomatic patients.

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H160

Iron status in a cohort of children with sickle cell disease on a chronic red cell exchange.

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Chronic Red cell exchange (RCE) may be used to treat the complications of Sickle cell Disease (SCD) and to manage transfusion associated iron overload. Iron chelation may also be required. Iron deficiency is less likely in patients on regular transfusion. There is minimal guidance on management of iron deficiency in SCD.

Aim: An audit was undertaken to describe the iron status, and treatment for a cohort of children with SCD requiring chronic RCE at The Royal Children's Hospital.

Method: A retrospective audit of iron status as determined by serum ferritin, change in ferritin and Ferriscan ® of children requiring chronic RCE was undertaken (Jan 2015- Jan 2021). Clinical and laboratory details at commencement of RCE program was compared with the last visit (Jan 2021 or transition).

Results: 278 RCE procedures were performed in 10 children with SCD. Ferritin was stable/reduced in 5 patients. Iron deficiency (ferritin < 20 ug/L) developed in two patients, both adolescent males treated with oral iron to manage symptoms. Reduction in hepatic iron overload was observed in 2 patients, with maintenance of normal hepatic iron in 3 patients.

4 patients were able to cease or hold oral iron chelation while continuing RCE. No patient had evidence of cardiac iron deposition on Ferriscan ®. No patients required escalation to dual iron chelation. 2 patients were commenced oral iron chelation and 2 patients remain stable without iron overload.

Conclusion: Chronic RCE was observed to assist in the management of transfusion associated iron overload in half of the cohort of children with SCD. Iron deficiency was observed in some patients. Clinicians should be alert to facilitate a hold on oral iron chelation given the increased risk of chelator toxicity. Oral iron supplementation was effective with good symptomatic benefit. Parenteral iron therapy may also have a role, though at increased cost/risk of adverse events. Further studies are needed to compare effectiveness of oral versus parenteral iron replacement and to determine the incidence of RCE associated iron deficiency in SCD.

H161

Australia-wide Haemoglobinopathy Molecular Testing Audit

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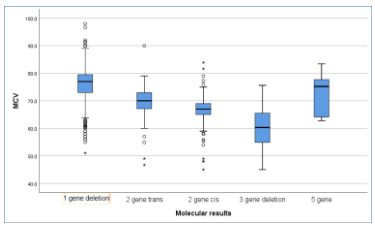
Aim: Antenatal screening for haemoglobinopathy carriers is standard of care in high risk populations to identify at risk pregnancies and provide genetic counselling and the option of antenatal diagnosis. The aim of this study was to complete a thorough and comprehensive review of antenatal haemoglobinopathy screening in Australia focusing on the correlation between baseline parameters and subsequent molecular testing. We aimed to assess the adequacy of international best practise guidelines for clinical screening and laboratory testing in our local population given the unique migration patterns in Australia.

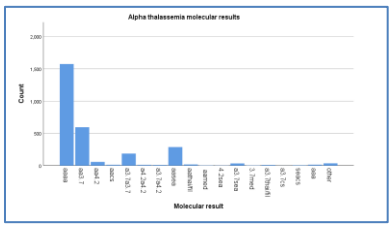
Method: A multicentre, retrospective audit of haemoglobinopathy screening and molecular testing over a 5-year period was undertaken. Deidentified data was collected in patients who underwent molecular testing with data collected on baseline demographics, red cell indices, haemoglobinopathy screening results and molecular testing results. Data was collated using REDcaps with SPSS statistics used for data analysis.

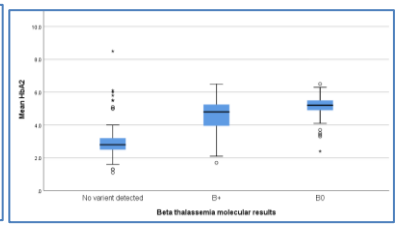
Results: 3155 cases across a 5-year period were identified aged between 2-89 years old. 46% of cases with alpha thalassemia testing had an alpha thalassemia deletion with 2 gene deletions in cis formation more common than trans (24% vs 15.7%). This demonstrates the high risk nature of the Australian population with the increased proportion of 2 gene cis mutations more pronounced in NSW relative to QLD. Mean haemoglobin, MCV, MCH and RCC can be seen in Figure 1 with the frequency of molecular mutations shown in Figure 2. 87% of cases with an alpha thalassemia deletion had a MCV <80 while only 66% had an MCV <76. ICT testing had a sensitivity of 69% and specificity of 81% when correlated with molecular testing (PPV 81.9%, NPV 68.2%) which was superior to HbH prep in some areas (sensitivity 56%, specificity 92%, PPV 93%, NPV 52.8%).

Correlation of beta gene variants and mean HbA2 is shown in figure 3. 11% of cases with beta haemoglobinopathies had a coexistent alpha thalassaemia mutation with single gene deletions the most common (70% of cases).

Conclusion: These results demonstrated a genetically diverse population with a significant proportion of 2 gene cis alpha thalassemia variants which carry the risk of hydrops fetalis in pregnancy. In addition, a substantial proportion of beta thalassemia cases carry a coexistent alpha thalassemia gene deletion which may go undetected relying on MCV and screening tests alone. Further modelling will be undertaken to assist in the development of a national consensus guideline regarding the role and indications for molecular testing in antenatal haemoglobinopathy screening.
Figure 1-3 (left to right)







Full blood count indices as a predictor of hospitalisation in patients with COVID-19, a Victorian Experience

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Aim: The COVID-19 pandemic has placed significant pressure on healthcare systems. Prognostic factors are needed to aid clinicians in deciding which patients need hospital admission. We set out to assess the relationship between Full Blood Count (FBC) parameters in COVID-19 positive patients and the need for hospital admission.

Method: A retrospective audit of adults with confirmed SARS-CoV-2 infection who had an FBC performed within 2 days prior and 14 days after their first positive SARS-CoV-2 swab and were managed through Northern Health, between March and September 2020. FBC parameters and the location of patient management were collected from the electronic medical record and laboratory information systems. Results were analysed using an independent t-test.

Results: 231 patients were identified. 177 patients were inpatients and 54 were outpatients. The mean number of days between positive swab and FBC was 2.05 days. Lymphocyte count was lower in those managed as inpatients than as outpatients (mean 1.2 ± 0.7 vs 1.5 ± 0.6 $x10^9$/L; p=0.006). Inpatients had higher neutrophil counts than outpatients (mean 5.2 ± 3.3 vs 3.5 ± 1.9 $x10^9$/L; p= <0.001). The neutrophil-to-lymphocyte ratio was higher in inpatients than outpatients (mean 6.84 ± 9.75 v 3.17 ± 3.49; p=0.007). Haemoglobin levels were lower in inpatients than outpatients (mean 132 ± 20 v 139 ± 17 g/L; p=0.020). No difference in platelet count was observed between the two groups (mean 231 ± 83 vs 224 ± 66 $x10^9$/L; p=0.569).

Conclusion: Patients who were hospitalised with COVID-19 infection were more likely to have lower lymphocyte counts and haemoglobin levels as well as higher neutrophil counts and neutrophil-to-lymphocyte ratios than those who were managed as outpatients. This suggests that these easily available FBC parameters could prospectively be used to help predict the need for hospitalisation in SARS-CoV-2 positive patients early in their illness.

A single-centre review of iatrogenic anaemia in adult intensive care

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Aim: Iatrogenic anaemia is an important problem amongst intensive care unit (ICU) patients, with significant daily diagnostic blood loss (DBL). Objectives: (a) To quantify the volume of DBL and evaluate its impact on ICU patients, (b) examine the correlation between severity of disease and DBL and (c) identify potentially vulnerable patient subgroups.

Method: A single-centre observational cohort study was conducted at St George's Hospital, London, cardiac and general ICU. Forty patients were included in the study. Variables measured were volume of blood collected and discarded on a daily basis, Acute Physiology and Chronic Health Evaluation (APACHE) II score, frequency of phlebotomy, haemoglobin concentration before and after admission to ICU, reason for admission and complications developed in ICU. The data were analysed using analysis of variance (ANOVA), independent t test (two-tailed) and Pearson correlation coefficient (using P < .05 to determine statistical significance) to examine the association between different variables and the volume of blood taken for phlebotomy.

Results: Mean (SD) total volume drawn per patient per day over 4 days was 86.3 mL (19.58). Nearly 30% of the total blood taken was discarded. There was a strong positive correlation between patients admitted because of sepsis and volume of DBL ($P < .01$), APACHE II score and volume taken ($P = .01$), patients who developed respiratory failure requiring ventilation and volume taken ($P < .01$) and patients who had received a blood transfusion and volume taken ($P < .01$). Haemoglobin concentration on discharge was negatively associated with DBL volume ($P < .01$).

Conclusion: High volumes of blood were taken and discarded from the study population. A way of addressing this in the future would be to devise guidelines to standardise the amount of blood that needs to be withdrawn in order to “prime” access lines.

Bevacizumab for Hereditary Haemorrhagic Telangiectasia

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Background: Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) involved in angiogenesis (1). It is predominantly used for solid organ malignancies and in countering neovascularisation in certain eye diseases (1,2). Overexpression of VEGF in patients with HHT has supported the case for use of Bevacizumab in managing severe and recurrent bleeding (3,4,5).

Case Report: BT, a 55-year-old male with HHT and a family history of symptoms in three generations, was referred to our service in May 2017. His ferritin was 6 mcg/L and haemoglobin 78 g/L. He was medically retired due to daily epistaxis. Investigations had confirmed gastric telangiectasia and a pulmonary arteriovenous malformation. His dominant symptoms were from unrelenting epistaxis that had commenced insidiously only since his late 30s.

Septodermatoplasty and sphenopalatine artery ligation in April 2018 reduced the severity of bleeding, but he remained iron deficient despite bimonthly parenteral ferric carboxymaltose.
From March 2019, he commenced Bevacizumab 5 mg/kg intravenously for four doses every fortnight, then monthly for a total of eight doses. This induction reduced the episodes and volume of epistaxis, improved cutaneous telangiectasias, and corrected iron deficiency anaemia. In the five years before Bevacizumab, he had been admitted to hospital nine times for severe epistaxis. He had received 22 units of packed red blood cells prior to induction. Since induction, he has not required re-hospitalisation, or any further blood transfusions.
However, within 12 months of completing induction, he experienced recurrence of bleeding and required additional iron infusions. Reinduction with Bevacizumab commenced in November 2020 with good effect and we plan for ongoing maintenance doses. His iron stores are now replete again and he has returned to premorbid function.
Conclusion: Although not curative, Bevacizumab has reduced hospitalisations and blood transfusions in this patient with HHT.

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H165

Gelatinous transformation of the marrow: Eating disorder diagnosed by bone marrow examination.

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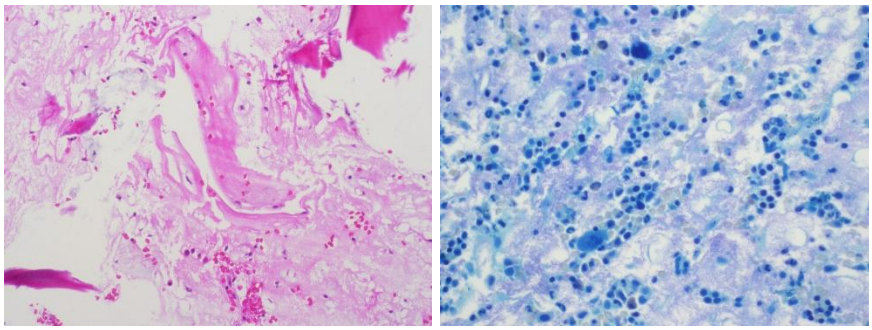
Aim: To be aware of psychiatric conditions manifesting with abnormal haematological parameters. In this case, an eating disorder was diagnosed based on a bone marrow examination.

Method: Clinical and laboratory data from a case report is described. The literature was examined for previously reported cases with similar clinicopathological features.

Case: A 21 y.o male referred from his GP for outpatient haematology review for the workup of neutropenia. Apart from a low BMI of 12.8, there were no other clinical diagnostic features of an eating disorder on initial assessment. FBE showed Hb 126 g/L, WCC 2.0 /nL, Neutrophils 0.8 /nL, Platelets 225, with no diagnostic features on blood film. CT imaging revealed no evidence of occult malignancy. Bone marrow examination revealed gelatinous transformation of the marrow.



He was subsequently referred for inpatient management under a physician specialising in eating disorders. Ongoing psychiatric and psychological input in conjunction with the initiation and weaning of nasogastric feeding, resulted in an improvement in nutrition which was associated with an improvement in the observed haematological parameters.

Conclusion: Gelatinous transformation in the marrow has been previously described in conditions associated with marked weight loss and anorexia, including malignancy and chronic infections, as well as psychiatric eating disorders. This case highlights the importance of clinicopathological correlation in atypical presentations of psychiatric conditions.

H166

Laboratory characteristics & clinical outcomes of COVID-19 infection among hospital inpatients, a Victorian experience

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Aim: Infection with the severe acute respiratory syndrome cononavirus-2 (SARS-CoV-2) is a global pandemic with significant morbidity and mortality. We aim to identify laboratory factors associated with poor prognosis for hospitalised patients with COVID-19.

Method: Retrospective audit performed of adult inpatients with confirmed COVID-19 infection at Northern Health, a tertiary hospital, between March and September 2020. Patient demographics, first laboratory results available on admission, treatment, qSOFA (a score to predict mortality for sepsis which includes altered mental status, respiratory rate ≥22/minute, systolic blood pressure ≤100mmHg) and clinical outcomes were collected through electronic medical records and laboratory information system.

Results: 199 cases were identified (median age 70 years [range 18-98], 97 [49%] male). 63 patients (35.2%) were from residential care. The most common treatments were antibiotics n=120 (60.3%), glucocorticoids n=87 (43.7%) and antivirals n=12 (6.0%). Of the 121 (60.8%) patients assessed as suitable for intensive care as per initial goals of care, 20 (16.5%) were admitted to ICU with 16/20 (80%) requiring invasive ventilation. 174 (87.4%) received prophylactic or therapeutic dose anticoagulation. There were four incidences of venous thrombosis (2.0%) including one pulmonary embolism. COVID-19 associated mortality rate was 20.6% (n=41) of which 31 (75.6%) were residential care residents. Only one patient deemed suitable for ICU admission (0.8%) succumbed. COVID-19 related mortality was associated with older age (median 85 vs 62 years), residential aged care status, goals of care not for ICU, high qSOFA score (scores 2-3) at presentation (p<0.001) and estimated Glomerular Filtration Rate (eGFR) <30mL/min/173m^2 (p=0.029). Non-survivors had lower admission lymphocyte count (median 0.85 vs 1.0 x10^9/L, p=0.010).

Conclusion: COVID-19 associated mortality was higher in the elderly and those from residential care reflecting underlying significant co-morbidities. The non-survivors were more likely to have a high qSOFA score, lower lymphocyte count and eGFR <30mL/min/173m^2.

	Total (n=199)	Survivors (n=158)	Non-survivors(n=41)	p-value*
Male	97 (48.7%)	73 (46.2%)	24 (58.5%)	0.16
Age (years)	70 (48, 84)	62 (44, 78)	85 (79, 91)	**<0.001**
Residential care	63 (35.2%)	32 (20.5%)	31 (75.6%)	**<0.001**
Goals of care for ICU admission	121 (60.8%)	120 (75.9%)	1 (2.4%)	**<0.001**
ICU admission	20 (10.1%)	19 (12.0%)	1 (2.4%)	0.067
High qSOFA score+	34 (17.1%)	20 (12.7%)	14 (34.1%)	**0.001**
Lymphocyte (x10^9/L)	1.0 (0.75, 1.5)	1.0 (0.8, 1.6)	0.85 (0.6, 1.1)	**0.010**
Neutrophil (x10^9/L)	4.5 (3.0, 6.4)	4.4 (3.0, 6.2)	5.4 (2.7, 7.1)	0.09
CRP (mg/L)	54 (13, 100)	45 (12, 91)	63 (16, 117)	0.05
D-dimer (mg/L FEU)	0.65 (0.44, 1.11)	0.65 (0.43, 1.05)	1.14 (0.6, 2.57)	0.14
Ferritin (µg/L)	328 (164, 834)	340 (170, 922)	257 (130, 690)	0.24
eGFR <30 (mL/min/1.73m^2)^	17 (8.5%)	10 (6.3%)	7 (17.1%)	**0.029**

Results reported as n (%) or median (interquartile range). *P-values calculated with Mann-Whitney U Test with p<0.05 significant
+qSOFA score: quick Sepsis Related Organ Failure Assessment. ^eGFR: estimated Glomerular Filtration Rate

H167

Predictors of clinical outcomes in residential aged care residents admitted to hospital with COVID-19 infection

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Aim: COVID-19 infection is a global pandemic with residential aged care residents at increased risk of infection and severe disease. We aim to identify clinical and laboratory factors associated with clinical outcomes in COVID-19 infections in this population.

Method: Retrospective audit performed of residential aged care residents with confirmed COVID-19 infection admitted to Northern Health, a tertiary hospital, between March and September 2020. Laboratory information systems and electronic medical records were utilised to collect patient demographics, comorbidities, first laboratory results available from admission, treatments and clinical outcomes.

Results: 63 patients were identified with median age 85 years (range 70-98) and 22 (34.9%) males. Patients had significant medical comorbidities including cognitive impairment/dementia in 41 (65.1%) and only 3 (4.8%) were documented as suitable for intensive care unit (ICU) admission. Seven patients (11.1%) were treated with palliative intent from presentation. 35 (55.6%) patients received antibiotics, 26 (41.3%) received glucocorticoid steroids. No patients were admitted to ICU. The mortality was high at 49.2% (n=31) and associated with male gender (p=0.027), chronic obstructive pulmonary disease (<0.001), high qSOFA (sepsis mortality prediction tool) score (p=0.020) and glucocorticoid use (p=0.03). Non-survivors had lower lymphocyte count (median 0.8 vs 1.1 $x10^9$/L, p=0.008). Other medical comorbidities, neutrophil count, eGFR <30 (mL/min/1.73m^2), CRP, D-dimer and ferritin were not associated with increased mortality. Of the survivors, 1 episode of post-discharge pulmonary embolism was captured.

Conclusion: The vast majority of aged care residents were assessed as unsuitable for ICU admission from time of presentation. COVID-19 associated mortality was high with non-survivors more likely to be male, have COPD, high qSOFA score and lower lymphocyte count. Glucocorticoid use was associated with higher mortality rate though may be reflective of treatment use in critically unwell patients.

Results reported as n (%) or median (interquartile range). *P-values calculated with Mann-Whitney U Test, p-value <0.05 significant. +qSOFA score: quick Sepsis Related Organ Failure Assessment ^COPD: chronic obstructive pulmonary disease %eGFR: estimated glomerular filtration ratio

	Total (n=63)	Survivors (n=32)	Non-survivors (n=31)	p-value*
Age (years)	85 (78, 88)	85 (78,88)	85 (79, 92)	0.24
Male	22 (34.9%)	7 (21.9%)	15 (48.4%)	**0.027**
Cognitive impairment	41 (65.1%)	20 (62.5%)	21 (67.7%)	0.09
COPD^	6 (9.5%)	0	6 (19.4%)	**<0.001**
Hypertension	45 (71.4%)	22 (68.8%)	23 (74.2%)	0.63
Diabetes	21 (33.3%)	12 (37.5%)	9 (29.0%)	0.48
Heart failure	15 (23.8%)	5 (15.6%)	10 (32.3%)	0.12
High qSOFA score+	8 (12.7%)	1 (3.1%)	7 (22.6%)	**0.020**
Antibiotics	35 (55.6%)	18 (56.3%)	17 (54.8%)	0.11
Glucocorticoid	26 (41.3%)	9 (28.1%)	17 (54.8%)	**0.032**
Lymphocyte ($x10^9$/L)	0.9 (0.6, 1.6)	1.1 (0.8, 2.0)	0.8 (0.5, 1.0)	**0.008**
Neutrophil ($x10^9$/L)	5.0 (3.0, 6.5)	4.7 (3.1, 6.8)	5.4 (2.7, 6.5)	0.46
CRP (mg/L)	62 (14,113)	50 (13, 100)	68 (16, 126)	0.22
D-dimer (mg/L FEU)	1.02 (0.37, 1.96)	0.98 (0.61, 1.75)	1.14 (0.54, 3.92)	0.07
Ferritin (µg/L)	314 (137, 576)	321 (152, 473)	275 (123, 683)	0.21
eGFR<30(mL/min/1.73m^2)%	6 (9.5%)	2 (6.3%)	4 (12.9%)	0.37

H168

Validation of a next generation sequencing based assay for T-cell receptor clonality detection in molecular diagnostics

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Introduction: T-cell receptor (TCR) clonality testing is useful in aiding the diagnosis of clonal lymphoproliferative disorders. Currently, the gold standard method is PCR amplification of the TCR gene followed by capillary electrophoresis (CE), which separates PCR products based on size. Here, we use novel next generation sequencing (NGS) technology to examine TCR clonality. Our aims were to determine the utility of NGS in TCR clonality testing and to compare the CE and NGS techniques.

Method: DNA samples (bone marrow, peripheral blood, FFPE tissue) were analysed using the LymphoTrack® Dx *TRG* Assay Panel - MiSeq (Invivoscribe, inc.) to detect TCR gamma (*TRG*) gene rearrangements. The *TRG* locus was amplified using primers targeted at the conserved variable and joining gene segments. Target genes were sequenced on the Illumina® MiSeq and data analysis undertaken using the LymphoTrack® Dx MiSeq® Software. Sequence clonality determination was defined as >2.5% of the total reads and >2x the read frequency for the third most frequent sequence when the sample surpasses a read threshold of 20,000.

Results: The concordance rate between the CE and NGS methods was 79.3% (23/29). 5 cases were found to be polyclonal using NGS which were previously reported as monoclonal or oligoclonal using CE. 1 case was found to be monoclonal (2 populations identified) on NGS, previously reported as oligoclonal with CE. Clinical history, results of other ancillary testing (morphology, flow cytometry) and long-term patient follow up correlated better with the NGS results.

Conclusion: NGS distinguishes between gene rearrangements based on unique sequences, whilst CE methods separate gene rearrangements based on size. With CE, there is a potential to inaccurately call two distinct, non-clonal rearrangements with the same size a monoclonal population. Our results demonstrate that T-cell receptor clonality detection by NGS offers a more sensitive and specific overview of a patient's T-cell repertoire in comparison to CE. Furthermore, knowledge of the clonal sequence can be used downstream for measurable residual disease (MRD) monitoring.

Clinical complications and hospital admissions in Australian patients with sickle cell disease in the Haemoglobinopathy Registry

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Nelson A, Haysom H, Waters N, Mason K, Kaplan Z, Greenway A, Chee M, Teo J, Kidson-Gerber G, Barbaro P, Cole-Sinclair M, Wellard C, Ho PJ, Wood E on behalf of the Sickle Cell Project Working Group and the steering committee and investigators of the National Haemoglobinopathy Registry

Aim: To describe clinical complications and emergency department/hospital admissions for sickle cell disease (SCD) patients in Australia using the Australian Haemoglobinopathy Registry (HbR).

Method: Analysis of HbR data on complications and hospital presentations for 314 SCD patients from 10 sites across Australia. Inclusion criterion was presence of a significant sickling disorder.

Results: For 12 months preceding last clinic visit:

- Acute complications were reported in 82% patients (74% paediatric patients, 95% adults). Most frequent were painful vaso-occlusive crises (VOC, 71% overall, 61% paediatric, 87% adults), infection requiring hospitalisation (28% overall, 30% paediatric, 25% adult) and acute chest syndrome (17% overall, 16% paediatric, 20% adults). Splenic sequestration (17% paediatric, 10% adult), dactylitis (8% paediatric, 3% adult), infection requiring hospitalisation and hyper-haemolytic crises (3% paediatric, 2% adult) were reported more frequently in children.

Chronic complications were reported in 33% patients (15% paediatric, 62% adult), the most common being chronic pain (0.6% paediatric, 37% adult), avascular necrosis (5% paediatric, 18% adult) and neurocognitive impairment (4% paediatric, 5% adult).

38% of all patients presented to a hospital ED; where these presentations were attributed to SCD, most common reasons were VOC (51% of patients who presented to ED) and infection (31%). Hospital admissions were reported for 39% patients; where these were attributed to SCD most common causes were VOC (49% paediatric, 58% adult), and infection (39% paediatric, 10% adult); acute splenic sequestration was more common in paediatric patients (6%) but all other causes were more frequent in adults. Many acute complications were managed outside hospital.

Longer term: History of sepsis (4.4% paediatric, 35% adult), cholecystectomy (4% paediatric, 37% adult) and splenectomy (9% paediatric, 25% adults).

Conclusion: SCD is a significant cause of morbidity in Australia, requiring substantial hospital support. Reported complications increase with age, with implications for patient care and health service planning.

Sickle cell disease in Australia: A snapshot from The Australian Haemoglobinopathy Registry in 2021

Dr Anna Nelson[1,2], *Mrs Helen Haysom[1], Dr Kylie Mason[3], Mr Neil Waters[1], Dr Zane Kaplan[1,4], Dr Anthea Greenway[1,5], Ms Melissa Chee[1], Dr Juliana Teo[6], Dr Giselle Kidson-Gerber[7], Dr Pasquale Barbaro[8], Dr Cameron Wellard[1], Dr Merrole Cole-Sinclair[9], Professor Phoebe Joy Ho[2], Professor Erica Wood[1,4]*

[1]Monash University, Melbourne, Australia, [2]Royal Prince Alfred Hospital, Camperdown, Australia, [3]Royal Melbourne Hospital, Parkville, Australia, [4]Monash Health, Clayton, Australia, [5]Royal Children's Hospital, Parkville, Australia, [6]Children's Hospital Westmead, Westmead, Australia, [7]Prince of Wales Hospital, Randwick, Australia, [8]Queensland Children's Hospital, South Brisbane, Australia, [9]St Vincent's Hospital Melbourne, Fitzroy, Australia

Nelson A, Haysom H, Waters N, Mason K, Kaplan Z, Greenway A, Chee M, Teo J, KidsonGerber G, Barbaro P, Cole-Sinclair M, Wellard C, Ho PJ, Wood E on behalf of the Sickle Cell Project Working Group and the steering committee and investigators of the Australian Haemoglobinopathy Registry

Aim: To describe the epidemiology, management and clinical outcomes of patients with sickle cell disease (SCD) in Australia as part of the Sickle Cell Project of the Australian Haemoglobinopathy Registry (HbR).

Method: Analysis of data from 10 HbR sites across five Australian states, including demographics, clinical characteristics, management, transfusion history, complications and resource utilisation. Inclusion criterion for SCD patients in the HbR is the presence of a significant sickling disorder. Participation in the HbR is voluntary using an opt-off consent model.

Results: Of 314 participants, 190 (61%) were children <18 years and 124 (39%) adults. 50% were female. 70.1% were born in Australia. Ethnicity was reported as 58.8% sub-Saharan African, 28.4% North African/Middle Eastern, 10.1% South/East European, 2.4% South/Central Asian, and 1.3% other.

Genotype was reported as 72.6% HbS homozygotes, 18.2% sickle/beta thalassaemia compound heterozygotes, 7.3% compound heterozygotes HbS/HbC, and 1.9% had another sickling disorder.

Most (65.8%) patients were transfusion independent, with 32.9% receiving regular red blood cell (RBC) transfusion and 1.3% occasional transfusion. Of those regularly transfused, 61.3% received automated exchange transfusion, 17% manual exchange, and 21.7% top-up only. RBC allo-antibodies were detected in 11% of participants.

55% of participants received hydroxyurea (58% paediatric, 50% adult) and 53% received prophylactic antibiotics (57% paediatric, 46% adult). Iron chelation therapy was reportedly only used by 12% (6% paediatrics, 21% adults). One participant had received an allogeneic stem cell transplant.

The complications of SCD and presentations to hospital are presented elsewhere.

Conclusion: Of the patients represented in the HbR, the majority were children born in Australia of African and Middle-Eastern ethnicity. HbSS genotype was the most common. Hydroxyurea and prophylactic antibiotics were widely used. One third of patients received regular RBC transfusion. These HbR data will be valuable for SCD patient care and health care planning.

H171

Pregnancy associated platelet autoantibody in MYH9 macrothrombocytopenia

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The MYH9-related macrothrombocytopenias are a cluster of rare, autosomal dominant platelet disorders. The degree of thrombocytopenia is often mild but can be severe; though bleeding complications are infrequent. Pregnancy and birth present challenges for these women with risk of haemorrhage at the time of birth of greatest concern. However, these women can also become sensitised during pregnancy, developing antiplatelet alloantibodies with HLA antibodies the most common, which can increase the challenges of platelet support at the time of bleeding challenges. Provision of HLA compatible platelets is suggested, where possible, at times of bleeding or invasive procedures to prevent the formation of alloantibodies. Autoantibodies in the setting of MYH9 disorders have not been described.

We describe a rare case of the development of an antiplatelet autoantibody, with specificity against the glycoprotein IIb/IIIa receptor, detected during pregnancy in a patient with known MYH9 platelet disorder. The 42-year-old woman with a background of Sjögrens disease, underwent repeat HLA antibody screening in her second pregnancy. Investigations to exclude FNAIT were also performed, due to her history of previous platelet transfusions, pregnancy and the rare but documented association of HLA antibodies with this condition.

The patient did not require any intervention during pregnancy and received HLA-matched platelets at the time of birth. Intravenous immunoglobulin was discussed as a potential therapeutic option predominantly in the event of FNAIT, but also as a therapeutic trial if the new autoantibodies exacerbated her thrombocytopenia. The platelet count however remained stable, and platelets incremented appropriately at time of transfusion.

We describe a case of antiplatelet autoantibodies in a pregnant woman with MHY9 platelet disorder, with Sjögrens disease postulated to be a potential contributor. Whilst autoantibodies have the potential to exacerbate pre-existing thrombocytopenia this was not seen in our case. Whether this autoantibody produces clinically significant thrombocytopenia remains to be seen.

Head-to-head comparison of human induced pluripotent stem cell (iPSC) haematopoietic differentiation methods for cost, efficiency, and sensitivity to model genetic disorders.

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Aim: Direct comparison of four iPSC haematopoietic differentiation methods for efficiency, cost, and utility to detect aberrant haematopoiesis.

Method: A commonly cited, efficient, serum- and feeder-free iPSC haematopoietic differentiation method was selected for improvement to reduce reagent cost and required hands-on time. Optimisation included reduction in the number of media changes, and addition of cytokines directly to the media. Characterisation of the improved method included multicolour flow cytometry (t-test), colony forming unit (CFU) assays, 2 methods of subsequent erythroid differentiation, time course studies, and capacity to detect aberrant haematopoiesis from B-thalassemia-derived iPSC. Direct comparison of four methods included independent replicates of up to 14 iPSC lines, number of live cells produced, multicolour flow cytometry, CFU assays, relative globin expression, reagent cost and hands-on time to produce 1 million CD34+ or CFU cells, and capacity to detect aberrant haematopoiesis from Down-syndrome-derived iPSC.

Results: The improved “2D-multistep” method resulted in a 7x greater efficiency in production of CD34+ (p<0.001) and haematopoietic progenitor cells (p<0.05, t-tests) at 50% cost of the original method. Of the four distinct methods, the improved 2D-multistep resulted in the greatest production of live cells, CD34+ progenitor cells, and functional haematopoietic progenitor cells (all p<0.001, ANOVA), while also doing so at the lowest cost and fewest hand-on hours per million progenitors produced. The 2D-multistep method also demonstrated the greatest sensitivity to recapitulate the haematopoietic phenotype of Down syndrome (p<0.001) and the capacity to recapitulate B-thalassemia (p<0.05, t-tests).

Conclusion:
Direct comparison demonstrated the improved 2D-multistep iPSC haematopoietic differentiation method was the most efficient at generating CD34+ and functional haematopoietic progenitor cells, while also being the most time- and cost-efficient, and most accurately recapitulating phenotypes of genetic haematopoietic disorders.

H173

Knowledge, Misinformation and Motivations about Blood Donation among Pharmacy Students in Hyderabad, Pakistan

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Aim: Blood donation is the only therapy to save life for many disease related to Blood. There is clear difference of the practices of blood donation between developed and underdeveloped countries. Current study designed to analyse the knowledge, misunderstandings and motivations of blood donations among pharmacy students in Hyderabad, Pakistan

Method: A descriptive, cross-sectional study was designed among pharmacy students. Based on Rao-Soft formula, sample size was 217. The sampling technique was random and the duration of study was six months. A series of questions was asked related to knowledge, misunderstanding and motivation of blood donations. The data was analysed descriptively.

Results: Out of 217 samples, only 38 (17.51%) are donors and remaining 179 (82.49) are non-donors. The age of samples are from 18 to 24 years. 03 donors are donating regular basis, while 26 only once and 09 donors donate their blood twice. As far as knowledge is analysed, insufficient knowledge were obtained. More than 50 % responded to donate blood if family and friends in need while more than 27% said if camp is arranged in university. The important motivations factors to donate blood are family (52%), friends (285), and religious (17%). The most common misinformation was disease such as Aids, Hepatitis B and C are transferred and the percentage was 63%.

Conclusion: It was clearly reflects that knowledge are insufficient, misinformation is on peak while motivations is only family and friend. Proper awareness will be the only need of current scenario to tackle the situation with the help of continuous medical education

H175

Frailty, How Do I Define Thee: Setting Up and Operationalising a Geriatric Malignant Haematology Referral Pathway

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Aim: Frailty is an increasingly common and significant complicating factor in the management of haematology patients as the population ages and has been shown to be a significant prognostic factor for morbidity, mortality, and treatment-related toxicity across a variety of haematologic and solid organ malignancies. Sydney South West Area Local Health District and Liverpool Hospital are the tertiary referral centre for a rapidly growing population of >1 million people.

Method: Due to increasing population of elderly frail haematology patients in South West Sydney Local Health District, a new protocol was developed for streamlined Comprehensive Geriatric Assessment referral of elderly frail haematology patients.

This involved analysis of the current system, feasibility estimates and discussions, ongoing feedback and process development.

Results: In consultation with General Medicine/Acute Care Medicine and Allied Health, a robust framework with rapid turnaround time was feasible for Comprehensive Geriatric Assessment.

Patients were pre-screened using the Rockwood Clinical Frailty Scale and G8 score, with clear clinical criteria provided for further referral to a geriatrician and physiotherapist.

Information provided to haematologists included detailed assessment of frailty/fitness and useful data for treatment decision-making and optimisation in the outpatient setting. Multidisciplinary Allied Health assessment with recommendations and interventions were provided.

Conclusion: Comprehensive Geriatric Assessment to aid in decision making and optimisation of malignant haematology patients is feasible and useful in a large tertiary centre.

H176

Long-term treatment burden following allogeneic blood and marrow transplantation in NSW, Australia: a cross-sectional survey

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Aim: Allogeneic blood and marrow transplant (allo-BMT) is now clearly established as standard therapy for many life-threatening conditions. Recognition of the profound impacts of the long-term and late effects is ever-growing, as is the healthcare workload (treatment burden) of survivorship. The aim of this study was to quantify the treatment burden of long-term survival following allo-BMT, with regard to the range of health services (medical, dental and allied healthcare reviews, and hospital attendances), therapies (conventional and complementary) and investigations accessed by long-term transplant survivors.

Method: A large, multi-centre cross-sectional survey of adult allo-BMT survivors who were transplanted between 2000 and 2012 in NSW, and had survived at least 12 months. Participants completed six validated instruments and one purposed designed for the study, the Sydney Post BMT Study (SPBS). Descriptive statistics were used to quantify current medication use, medical treatments, referrals, assessments and frequency of hospital/clinic attendance.

Results: Of the 441 respondents, over a quarter who were more than 2 years post BMT attended the hospital clinic at least monthly, and 26.7% required a number of regular medical procedures (e.g. venesection, extracorporeal photopheresis). More than 20% were taking 6 or more medications daily, and 54% reported using at least one CAM. Specialist medical and allied health referral was very common, and compliance with internationally recommended long-term follow-up (LTFU) care was suboptimal and decreased as time from BMT increased.

Conclusion: Respondents reported a large medication (conventional and complementary), screening, assessment and health care burden. It must be acknowledged that treatment burden contributes significantly to the ‘workload’ of survivorship and can have a severe and negative impact on BMT survivors, carers and the healthcare system—making it difficult to comply with optimal care. Clinicians must be primed with skills to identify survivors who are overburdened by the health care required for survival and develop strategies to help ease the burden.

H177

A case of invasive Scedosporium Aurantiacum acute on chronic rhinosinusitis with Sellar turcica infection following Acute Myeloid Leukaemia induction therapy.

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Abstract: Invasive fungal infection (IFI) in acute myeloid leukaemia (AML) patients undergoing induction chemotherapy has been well described. Non-aspergillus, mould organisms, e.g. Candida, Mucor and Scedosporium species seem the most significant organisms with adoption of anti-aspergillus prophylaxis. While most common sites of invasion include the bloodstream and sinopulmonary, invasive central nervous system (CNS) infections are less common but recognised and associated with treatment failure and high fatality rates.

We report the case of a 64-year-old lady with a Scedosporium Sella turcica infection diagnosed during induction chemotherapy. An Indonesian migrant, she was diagnosed with myelodysplastic syndrome with del 5q in 2016 and subsequently commenced on lenalidomide in March 2020. After seven months, with progressive pancytopenia, she was noted to have transformed to AML and was admitted for induction chemotherapy with 7-3 protocol. As per unit protocol, she was commenced on anti-aspergillus but no mould prophylaxis.

Post induction recovery was complicated by Klebsiella Voriicola bacteraemia on day 8 requiring intensive care support. Febrile episodes were recurring by day 15 despite aseptic cultures and intravenous meropenem and vancomycin as antimicrobials. A dedicated CT brain and sinuses in the context of episodic hallucinations demonstrated an enlarged and empty Sella as well as bifrontal ethmoid sinus occlusion with right sphenoid sinus thickening. A nasoendoscopy was however non-diagnostic. She developed a candidemia by day 23 requiring addition of anidulafungin.

At day 34, with a drop in consciousness and cerebrospinal fluid rhinorrhoea, MRI noted a complex pituitary cyst which was biopsied for histopathology and mycology demonstrating a light growth of Scedosporium Aurantiacum. Voriconazole and terbinafine suppressive therapy was commenced but neurosurgical debridement was not feasible given the extent of bone and Sella involvement. Consequently, all further AML therapy was abandoned and despite complications of this IFI, she had a sustained disease remission for 5 months prior to deterioration.

H178

Deep immunophenotyping by spectral flow cytometry to get the most out of patient samples.

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Aim: Flow cytometry is the technique of choice for profiling a patient's immune landscape and identifying interesting trends for further investigation. Deep immunophenotyping using conventional flow cytometers requires multiple panels and reduces the amount of sample available for functional assays. We sought to reduce the demand on patient samples and improve phenotyping depth by developing a single immunophenotyping panel for use on new spectral flow cytometers.

Method: A flow cytometry panel was designed, using conventional panel design philosophy, based on two existing flow cytometry panels used on conventional flow cytometers to phenotype peripheral blood mononuclear cells (PBMCs). The expanded flow cytometry panel was designed for a five laser, sixty-four detector Cytek™ Aurora spectral flow cytometer. The panel was optimised for PBMC phenotyping, with healthy donor PBMCs used to validate the panel. Stimulated PBMCs were used to validate checkpoint marker detection.

Results: A 30 colour immunophenotyping panel was successfully designed for use on spectral cytometers. This panel increased the number of cell populations identified. The expanded panel matched or exceeded the old panels' capability (Figure) and added Treg-like cell identification and the capacity to measure PD-1, TIM3, LAG-3, ICOS, 4-1BB and PD-L2 expression. In addition to improved phenotyping, the use of a single panel reduced preparation and acquisition time, batch variation and halved the required amount of sample by reducing the number of panels from two to one.

Conclusion: The use of spectral cytometry for immunophenotyping increased phenotyping depth while simultaneously using less sample than previously required, which is crucial for functional analyses involving patients or timepoints with poor PBMC yield. The use of spectral cytometry will improve the laboratory's capacity to extract the maximum amount of data from often limited patient samples.

A

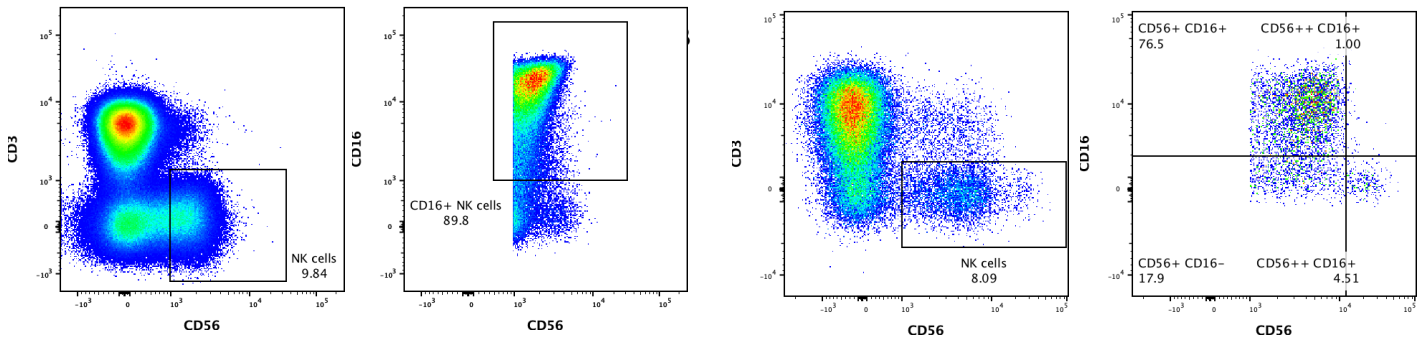

Figure: Comparison of Natural Killer cell Phenotyping

A comparison of A) conventional and B) spectral flow cytometry for NK cell phenotyping. Representative plots from two healthy donors shown.

Bone marrow aspirate and trephine biopsies: not so safe, and could be safer

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Aim: Bone marrow biopsies (aspirate and trephine) are essential for diagnosis and treatment monitoring in haematology, frequently performed in outpatient settings and presumed to be safe. The procedure is invasive and often performed under "conscious sedation" by junior staff. Annual surveys in the UK in the early 2000s[1-3] reported very low complication rates (<0.09%) but with suspected underreporting. No previous studies have explored the incidence of serious adverse events in the Australian context.

Method: All biopsy-related serious adverse events occurring over 8 years (Dec 2012 – Dec 2020) were identified prospectively at a single tertiary Australian hospital. Complications were deemed to be significant if resulted in admission or change in management, including significant laboratory errors, or led to proceduralist injury. CTCAE grading of event severity was performed if possible.

Results: Thirty incidents were identified from 9124 biopsy procedures (0.33%), 1 in 300 biopsies.

Excessive bleeding in 10 patients resulted from arterial injury requiring embolization (3 patients), unrecognised bleeding diathesis (4 patients) and unknown cause (3 patients). Over-sedation caused 7 events ranging from hypoxia to respiratory arrest. Hospitalization occurred for pain (2 patients), suspected nerve injury, infection, rigors/confusion and allergy (1 patient each). Peri-procedural events: laboratory error mandating repeat biopsy (3 patients), proceduralist blood exposure (2 needlestick injuries, 1 blood splash injury), "wrong patient" biopsy (1 case).
Of 24 clinical incidents, 20 (83%) were of grade 3-4 severity, four of these life-threatening.
Human error was causative in 30% of events. Two resulted in formal root cause analysis and change in institutional practice: introduction of a proceduralist training program following inadvertent sedative overdose, and "time-out" process after biopsy of incorrect patient.

Conclusion: Close, single institution surveillance has shown a much higher rate of severe bone marrow biopsy-related adverse events than was previously recognised. Physician training, formal protocols and understanding of bleeding risk factors are critical to maintain patient – and proceduralist - safety.

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H180

Minimising a high-risk patient cohort's hospital exposure during a pandemic- outcomes of a nurse-led transition from intravenous to subcutaneous immunoglobulin replacement

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Background: Patients with acquired hypogammaglobulinemia, secondary to cancer, are at high risk of complications of Sars-CoV2. To protect this vulnerable patient group, we transitioned our hospital based intravenous immunoglobulin (IVIg) program to a nurse-led subcutaneous immunoglobulin (SCIg) service. We will describe the feasibility and safety data for this service.

Methods: Patients with secondary hypogammaglobulinemia receiving Ig replacement were considered for SCIg by their treating haematologist. Patients were approached by and taught how to administer the SCIg by a haematology nurse. Where appropriate, training was outsourced to a SCIg-trained nurse who would attend the patient's home. Once proficient, patients were supported via the model of nurse-led care and a "drive through" medication pick-up service was put in place for patients to collect their Ig product. A retrospective audit of patients converted from IVIg to SCIg, from March 2020 to December 2020, was undertaken to examine feasibility and safety of the service. Patients were identified from a prospectively maintained database. Data were analysed descriptively.

Results: Of the 33 patients converted from IVIg to SCIg, eight (25%) commenced Ig therapy for the first time during the pandemic. Five (15%) of those transitioned were regional patients and product collection was organised in their local area. Reasons for patients not transitioning included: patient preference to remain on IVIg, patients with relapsed disease and hospital-dependant treatment. Only three patients (9%) had adverse events recorded, the majority relating to skin irritation at the injection site. No serious adverse events occurred. Seven patients (21%) discontinued SCIg; 12% due to patient preference.

Conclusions: The SCIg model was shown to be safe and feasible. However, further research is needed to explore possibility of drug delivery to patients' homes to prevent unnecessary travel to hospital for pick up, and to explore cost efficiency for patients, patient experience, and system level efficiency.

Audit of pre-analytic variables affecting yield of cerebrospinal fluid flow cytometry

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Aim: Identify pre-analytic variables affecting cell count and yield of flow cytometry performed on cerebrospinal fluid (CSF) samples.

Method: Audit performed prospectively in a single tertiary hospital with an inpatient haematology unit. Data was collected on patient demographics, indication for testing, time of specimen collection/arrival at central specimen reception/processing, volume of sample collected, medium within which specimen collected and if blood contamination present. Comparison to cytology result on each specimen was also performed.

Results: Data on 71 CSF samples for 38 patients was prospectively collected from June to November 2020. Indications for testing included central nervous system (CNS) staging for haematological malignancy (including high-grade lymphoma, acute lymphoblastic leukaemia and acute myeloid leukaemia) or evaluation in neurological disorders. Average volume collected was 2.3mL of fluid. All samples were sent in RPMI growth medium. 16 samples were visibly blood contaminated. Average time from sample collection to arrival at central specimen reception was 21 minutes. Average time from arrival at specimen reception to processing was 4 hours and 15 mins. Average time from collection to processing was 4 hours and 36 mins. 4 samples arrived late in the day and were processed the following day, while 67 samples were processed on the same day. An average of 1910 events were recorded per sample.

Conclusion: This audit identifies a high rate of routine RPMI use, rapid processing times and minimal blood contamination in CSF collection used for flow cytometry testing. A high number of events per sample is noted, however due to medical record destruction to hospital flooding, a comparison to event yield prior to the routine use of RPMI was umable to be performed.

International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction: a standardised approach to assessing kidney function in cancer patients and its application to anticancer drug dosing

Dr Geeta Sandhu[1], *Ms Niamh O'Neill*[1], *Ms Aisling Kelly*[1], *Ms Julia Shingleton*[1], *Ms Josephine Touma*[1], *Ms Evangeline Armstrong Gordon*[1], *Ms Liesel Byrne*[1], *Professor Robyn Ward*[1,2]
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Aim: Anticancer drug dosing recommendations in kidney dysfunction are often empirical, based on non-standardised creatinine assays calculated via the Cockcroft-Gault equation,[1] and lack applicability to globally accepted kidney dysfunction classifications. The guideline aims to provide a consensus-based standardised approach to the measurement of kidney function in cancer patients and its application to anticancer drug dosing.

Method: An expert international multidisciplinary guideline working group was established to develop drug dosing recommendations that were based on internationally accepted approaches in determining kidney function and classifying levels of dysfunction. Endorsement was sought from medical professional bodies and other key stakeholders in December 2020 via a national consensus workshop.

Results: Three critical recommendations were endorsed:

- Using estimated glomerular filtration rate (eGFR) via the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation[2] to guide the assessment of kidney function, except when directly measured GFR is necessary.
  1. Where anticancer medication dose is dependent on kidney function, eGFR is suggested to guide dosing.
  2. Application of international kidney dysfunction classification[3] to guide stepwise dose adjustments of anticancer drugs.

Conclusion: The eGFR using the CKD–EPI equation[2] is the most accurate and convenient method for assessing kidney function in diverse populations (including cancer patients) and accounts for the standardisation of the creatinine assay. This standardised approach reduces complexity of kidney function estimation, promotes uniformity of measurement and informs dosing calculations, to encourage consistency and safer delivery of anticancer treatment.

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International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction: anticancer drug specific recommendations on dose adjustment in kidney dysfunction

Dr Geeta Sandhu[1], *Ms Niamh O'Neill*[1], *Ms Aisling Kelly*[1], *Ms Julia Shingleton*[1], *Ms Josephine Touma*[1], *Ms Evangeline Armstrong Gordon*[1], *Ms Liesel Byrne*[1], *Professor Robyn Ward*[1,2]
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Title: International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction: anticancer drug specific recommendations on dose adjustment in kidney dysfunction

Aim: Paucity of data and global inconsistencies underpin current anticancer drug dosing recommendations in kidney dysfunction. Kidney dysfunction (12% incidence in cancer patients),[1] may alter the pharmacokinetics and pharmacodynamics of renally-eliminated anticancer drugs. The guideline aims to provide the first evidence-based, clinically driven recommendations on dose adjustment for anticancer drugs in kidney dysfunction.

Method: An expert international multidisciplinary working group was established to develop the guideline using internationally accepted guideline frameworks. Clinical questions were formulated to identify renal elimination and nephrotoxic potential of individual anticancer drugs during the literature search. The Grading of Recommendations Assessment, Development and Evaluation was used to critically appraise the quality and strength of the evidence and formulate recommendations by the working group. The working group anonymously voted on the acceptability of individual drug recommendations until consensus was achieved.

Results: The working group formulated evidence-based and clinical consensus recommendations for 59 drugs. National consensus recommendations on kidney function assessment were applied to dosing recommendations and a traffic light system for alerting clinicians to caution around levels of kidney function (Table 1).

Table 1. Example of an individual drug dosing recommendation

BLEOMYCIN DOSING RECOMMENDATION		
eGFR (mL/min/1.73m^2)	**Dose**	**Comment**
≥ 60	**Full dose**	
45-59		
30-44	**Full dose**	Consider alternative treatment in curative intent. Monitor for signs of pulmonary toxicity.
15-29	**Reduce by 25-50%** **or** **alternative treatment**	Consider alternative treatment in curative intent. Monitor for signs of pulmonary toxicity.
< 15 (without kidney replacement therapy)	**AVOID**	Not recommended. Consider alternative treatment.
Kidney replacement therapy	A multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology is recommended for the management of dosing.	

Conclusion: An internationally standardised approach aims to facilitate consistent anticancer drug dose adjustment in cancer patients with kidney dysfunction and safer delivery of treatments. Publication of the first edition of the guideline and implementation into eviQ protocols will ensure international dissemination and endorsement as a benchmark by regulatory bodies.

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Supporting best practice care with evidence-based education

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Aim: To support the delivery of best-practice care to people with haematological diseases by providing evidence-based, standardised education to health professionals involved in their care.

Method: In 2018, eviQ received requests to develop a centralised training resource which supports knowledge and skill development for clinicians working in haematology. A landscape and learning needs analysis was performed via survey to haematology professionals to identify available training resources and determine knowledge gaps.

Landscape analysis revealed that no training resources were available nationally. However, an outdated resource was identified within NSW.

A Delphi-type method was employed, and the existing paper resource was reviewed and redeveloped into a five-module online course. This process involved subject matter experts from eviQ and the ACI BMT network aligning the content with current evidence, followed by two rounds of review with haematology clinicians nationally.

Results: The first three modules of the *Introduction to haematology and blood and marrow transplantation* course were released on the eviQ Education website from December 2019.The course has since received 9,354 unique views.Course evaluations indicate that over 98% of users were either satisfied or very satisfied with the modules. After completing the learning, most survey respondents (>80%) also indicated that they had a ‘clear’ or ‘strong’ understanding of the topics covered.

Conclusion: The majority of learners completing the modules are highly satisfied with their learning experience and have a clear or strong understanding of learning concepts critical to delivering best practice, evidence-based care. Furthermore, development of the online course addressed the unmet need of a centralised learning resource for haematology clinicians.

A001 – A054: ANZSBT Posters

A001

Triggering the Massive Transfusion Protocol at Monash Health: who, when, why and what happens next?

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[1]Monash Health, Melbourne, , [2]Ballarat Health Service, Ballarat, Australia, [3]Monash University, Melbourne, Australia

Aim: Critical bleeding requiring major transfusion support occurs in diverse clinical settings, and is associated with major morbidity and mortality. Communication and documentation are essential to enable timely provision of blood component support and to limit blood wastage, and massive transfusion protocols (MTP) can help manage these complex events.

Method: Audit of electronic medical record (EMR) and hospital blood bank data for 34 consecutive MTP activations across Monash Health between 1 January - 31 March 2021. Results were compared with a baseline audit of 50 MTPs in 2018/2019, conducted prior to implementation of our EMR and an updated MTP.

Results: Median age was 54.3y (range 24-84); 59% of recipients were male. Surgical bleeding predominated (35.3% cases), followed by obstetrics/gynaecology (23.5%), gastrointestinal (20.6%), and other causes, including trauma (3%).

MTPs were most frequently activated in operating theatres (OT, 29.4%). Importantly, 50% of recipients moved locations during the MTP, most commonly to OT, ICU or interventional radiology. MTP activating details were clearly communicated and documented in 85.3% cases, up from 53% in the previous audit; however, notifying the blood bank of MTP deactivation remained suboptimal (29.4%).
Early (within 15 mins) and frequent pathology testing following MTP activation was performed only in 53% and 59% episodes, respectively. Point-of-care testing was used in 32% cases.
Of blood products issued, 89.2% were transfused, 10.8% returned and 4% discarded. Mean number of total units transfused was 13.6 per MTP (5.9 RBC, 2.6 FFP, 0.9 platelets, 4.6 cryoprecipitate). Successful haemostasis/recovery was documented in 79.4% cases, and 20.6 % patients died.

Conclusion: At Monash Health, most MTPs were activated for non-trauma clinical bleeding. Recipients frequently moved between locations during an MTP. Notification to blood bank occurred promptly. Blood component use was well balanced (although platelet and cryoprecipitate dosing was quite low), and wastage was minimal.

A002

Should we order a Kleihauer? An audit of the ordering and laboratory practices for fetomaternal haemorrhage assessment in a tertiary Australian hospital.

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Aim:
Estimation of the volume of fetomaternal haemorrhage (FMH) has been traditionally performed by the Kleihauer-Betke test (KBT). Although less sensitive than flow cytometry (FC), the KBT is widely available, doesn't require knowledge of fetal Rh D status and can be performed urgently. The goal of our study was to review the clinical indications, results and laboratory processes of the KBT in the context of local and international guidelines.
Method:
A retrospective audit was performed analysing 411 consecutive KBT requests received between November 2019 and March 2020 at a tertiary obstetric hospital. Laboratory and clinical records were reviewed, including maternal Rh D status, clinical indication for testing, urgency, dosing of Rh D immunoglobulin (if applicable), and notification of ordering clinician.
Results:
Interestingly, a detectable FMH (>0.96mL) was present in only 12% (44/375) of tests performed with a median of 2.6mL (1.92-4.09mL 95%CI). An FMH ≥5mL was detected in 3.5% (13/375) of cases with appropriate additional dosing of Rh D immunoglobulin administered in the Rh D negative cohort. A record of the ordering clinician being notified was present in 11/12 cases.
The clinical indication for testing was clearly documented in 83% (341/411) of cases. 27% (108/402) of evaluable requests did not meet the indication for testing criteria as per guidelines. Uncomplicated antepartum haemorrhage in Rh D positive women was the recorded indication for 54% (58/108) of requests not meeting indication criteria.
Conclusion:
Although uncommon, detectable FMH via KBT requires accurate and timely quantification. FMH ≥5mL, which may require additional doses of Rh D immunoglobulin, was detected in 13/375 cases. Our laboratory has appropriate processes to service this population and does not appear to be negatively impacted by absence of FC. Moreover, improved education of clinical staff will facilitate appropriate pathology testing, resulting in more effective use of healthcare resources.

A003

A Pandemic positive – virtual platforms facilitate greater opportunities for education and collaboration even across closed borders

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Background: The Blood Matters Scientist role is to assist with education/resources to support best practice and compliance in the areas of blood management for scientists. Traditionally education was primarily face to face. With the pandemic came changed work practices and education converted to virtual platforms.

Aim: To provide educational opportunities to transfusion scientists addressing current issues and topics through virtual platforms.

Method: Several virtual platforms were tested and evaluated for ease of use (presenters/participants), accessibility (across firewalls) and capability for interaction. Webex meetings provided the most suitable option.
To reduce possible duplication, discussion and collaboration occurred with other relevant parties.

Results: 2020 virtual education received overwhelming attendance, not only local (rural and regional), but also interstate colleagues across closed borders (at the time). While target audiences were scientists, attendance was multidisciplinary. Feedback was extremely positive and topics suggested were included in 2021 program, including collaborative sessions with peak bodies.
A significant issue for scientists is the new clinical trial - Magrilomab (anti-CD47 monoclonal antibody) interference with pretransfusion testing. Despite closed borders virtual collaboration was facilitated between senior scientists (Victoria), Lifeblood experts and ANZSBT representatives (across Australia). Resulting in:

- submissions to the Chief Trial Investigator to raise awareness.
    - ANZSBT guidance document drafted for approval and publication.
    - virtual education held - 175 sites online. Recording distributed for further education.

Evaluation response was excellent with resounding positive feedback for the topics, and support for ongoing virtual education even when travel restrictions have eased. Good attendance and feedback was also received for other education sessions provided.

Conclusion: Transition to virtual education has allowed it to be more accessible and inclusive, even extending beyond our borders. While the borders are now open the use of virtual platforms to provide opportunities to collaborate and communicate for best patient care will continue.

A004

Are the perioperative patient blood management (PBM) guidelines fully implemented after nine years?

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Background: Patients who are thoroughly prepared for surgery, through diagnosis and treatment of anaemia have improved rates of recovery and better outcomes (NBA/PBM Resource guide, 2018). Patient's own blood can be conserved though medical, pharmacological, anaesthetic and surgical strategies, which can reduce the need for transfusion.

Aim: To assess practice compliance to the PBM guidelines: Module 2; specifically, assessment and management of reversible anaemia prior to elective surgery where substantial blood loss is anticipated.

Method: Health services (140) from Victoria, Tasmania, Australian Capital Territory and Northern Territory were invited to audit up to 30 patients who had elective surgery (orthopaedic, gynaecologic, colorectal and cardiothoracic) focusing on preoperative assessment and management practices (Module 2).

Results: Current results were compared with a similar audit conducted in 2015 to identify improvements.
Comparison of 2020 and 2015 results.

Module 2 criteria	**2015 (n=1142)**	**2020 (n=1541)**
Documented as preoperatively screened*	93%	81%
Screening included: • FBE • Ferritin	 97% 25%	 96% 45%
Timely screening (>4 weeks prior surgery)	32%	40%
"Quality" screening (timely and pathology)	9%	20%
Anaemia/iron deficiency detected: • NBA Module 2 definition • Documented by health service	 20% 11%	 20% 8%
Treated for anaemia/iron deficiency for patients identified by health service: • Any treatment • Red cell transfusion alone	 48% 16%	 71% 12%
Reassessment after treatment prior to surgery	66%	62%
Anaemia resolved	9%	30%

*Documented as preoperatively screened not necessarily meeting Module 2.

Conclusion:
Although there is no improvement in the percentage of patients receiving preoperative screening, when performed a larger percentage were assessed comprehensively and treated. Recognition of anaemia remains poor against Module 2 definitions. Reassessment post-treatment remains similar, with more patients having anaemia resolved in this audit. While there are definite improvements, there are still gaps with only 20% of patients receiving quality assessment and 12% receiving red cells as the only treatment for anaemia.

A005

Improving blood safety with haemovigilance reporting to the Serious Transfusion Incident Reporting (STIR) Victoria?

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Background: Blood Matters serious transfusion incident reporting system (STIR) is a voluntary haemovigilance system in place since 2007, receiving reports on both clinical and procedural events related to transfusion. All data is de-identified.

Aim: Improve patient safety through analysis and feedback of haemovigilance events reported to STIR.

Method:

- Review and validation of all serious transfusion incidents reported to STIR by Expert group.
  - Incidents aggregated and reports distributed to reporting health services.
  - Annual report is published and circulated
  - Bulletins are distributed and published on incident trends or specific topical issues.
  - Data for all reporting jurisdictions are made available for inclusion in the National Haemovigilance report.

Results: Annual STIR reports published since 2014

- Changes to forms in response to issues raised and changes in practice
- Case studies to highlight important information
- Recommendations for practice improvement
- Quick and easy summary infographics
- Presentations for use.

Six Bulletins published since 2018.
Patient safety promotional campaigns; e.g. Transfusion Associated Circulatory Overload (TACO) was undertaken in 2017, highlighting risk factors and management.
Incident data prompted the practice audit of RhD immunoglobulin prophylaxis, which did highlight gaps in practice. The full report and recommendations are available. These gaps were also communicated through a publication in the specialist journal and at midwifery conferences.
Support tools and education based on case studies and repeated incidents from STIR have been produced to highlight best practice for specimen collection, blood administration and recognition and management of transfusion reactions.
Posters and oral presentations at conferences, both nationally and internationally, sharing insights from our program.
Conclusion: Haemovigilance is an important part of ensuring and improving patient safety. The STIR program uses the data to highlight areas of concern, promote best practice and improvements. Reports submitted improve our knowledge and provide opportunities to share those learnings with others in a wide range of formats.

A006

Occult alloimmunization to RhD related to graft versus host disease and its treatment

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Alloimmunization to RBC antigens post-allogeneic stem cell transplantation is rare - even to RhD which is very immunogenic.[1,2] Most alloimmunizations to RhD are detectable within a year with median time of detection a month after exposure.[3] We report anti-D detection in an allogeneic bone marrow transplant (BMT) recipient five years after last exposure to RhD-positive RBC.

Case Report: A 19 year old RhD-negative male with Wiskott-Aldrich syndrome (WAS) underwent an allogeneic BMT, following myeloablative conditioning (Bu/Cy/ATG), from an RhD-positive, HLA-matched, unrelated donor on 02 September 2015. Acute GvHD was treated with steroids and ATG. Chronic GvHD supervened requiring steroids, Mycophenolate, Cyclosporin, Imatinib, and Sirolimus, and, following GIT involvement at +15 months, Infliximab between +17 to +48 months. In November 2020, after being off Infliximab for 18 months, anti-D was found on pre-operative antibody screening.
Other than through one RhD-*positive* platelet unit on day -17, he had no exposure to RhD-positive RBC. IVIg was last given in November 2017, platelets, RhD-negative, in November 2015, and FFP/cryoprecipitate/RhD immunoglobulin, never. Therefore it is unlikely that the anti-D detected was passively acquired.

Discussion: This patient likely had occult alloimmunization of the *donor's* immune system to RhD. Since there was no exposure to RhD-positive RBC post-BMT, this likely happened, early post-BMT, through the *patient's* residual RhD-positive RBC, but remained undetected because of cGvHD, and immunosuppressive treatment especially Infliximab. Infliximab, among other things, impairs B cell maturation and T-dependent B-cell responses.[4] WAS itself may cause hypogammaglobulinaemia. Immunoglobulin levels were low, but corrected post-allo-BMT. Passenger Lymphocyte Syndrome may also explain the unexpected anti-D, but this patient had no risk factors (pre-sensitized donor, PBSCT, reduced intensity conditioning, and methotrexate exclusion from GvHD prophylaxis). Similar cases are rarely described in the literature.[5,6] RBC antibody screening should be performed after GvHD resolves and immunosuppressives are discontinued.

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A007

Primary or anamnestic antibody response to RhD after bone grafting: case report and implications

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Case Report: In August 2020, a group A RhD-negative woman aged 85 years, with complex and long-standing orthopaedic problems was found unexpectedly to have anti-D following a hip fracture. Two of four children born between 1962 and 1969 were known to be RhD-positive. In 1999, she had red blood cell (RBC) transfusions. Records are unavailable, but they were likely RhD-negative. In 2017, she received three RhD-negative RBC. In 2018, she received a bone allograft from an RhD-positive donor. Previous antibody screens (2018, 2017, and eight between 2013-2017) were negative. At no point had she received any RhD immunoglobulin, intravenous immunoglobulin or any other blood components.

Discussion: RBC in the RhD-positive bone allograft could have caused either primary alloimmunization, or an anamnestic response following primary alloimmunization during the pregnancies. Bone grafts – autologous or allogeneic - are commonly transplanted tissue. Although supposedly denuded of cells, RBC may be present in bony lacunae.[1,2] Even few RBC – such as in adult doses of platelets – can cause alloimmunization.[3] Frozen-thawed RBC are less likely than standard RBC to cause HLA alloimmunisation, but there is little information regarding immunogenicity of RBC antigens after freezing.[4] Reports are scanty, but humoral and cell mediated responses to antigens in bone allografts are known.[5,6]

Conclusions: With allografts likely to be contaminated with donor RBC, primary, and anamnestic antibody responses, and delayed haemolytic transfusion reactions must be considered, and the patient's transfusion and pregnancy history, and RBC phenotypes of patient, graft donor, and any concomitant RBC transfusions should be evaluated. Antibody screening should be performed after a reasonable interval. Prophylactic RhD immunoglobulin use with solid organ transplants appears patchy but should be considered for RhD-negative patients with child bearing potential receiving RhD-positive allografts including bone grafts (e.g. 500 - 625 iu within 72 hours).[7]

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A008

Impact of National Hemovigilance reporting system on Transfusion services at a private Hospital based blood bank in India

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Aim: This study was initiated to analyze the effectiveness of National Hemovigilance reporting system on blood transfusion practices at our blood bank.

Method: Data was collected over a period of 10 months between June2020 to March2021. As National Hemovigilance reporting system at our centre was initiated from November2020, the study period was divided into two groups. Group I included months from June2020 to October2020 and Group II included months from November2020 to March2021. The data related to number of donations, donor reactions, number of blood transfusions and transfusion reactions were compared between the two groups. Data was analyzed based on the objectives using descriptive and inferential statistics.

Results: All adverse reactions caused by transfusion of blood and its products during the study period along with the adverse donor reactions reported were included in the study. Group I had a total of 463 donations with no donor reaction reported, whereas group II had 537 donations with 2(0.37%) donor reactions. Similarly, Group I had a total of 1014 transfusions with 2(0.19%) transfusion reactions reported, whereas group II had 1381 transfusions with 10(0.72%) transfusions reactions. 40% of the transfusion reactions were allergic reactions to plasma components and 40% were febrile non hemolytic reacton to red cell transfusions. Remaining 20% were with only chills and rigors after blood transfusion.

Conclusion: The hemovigilance program of our institution helped in assessing the diversity of adverse reactions associated with transfusion of blood components. It helped in improving the reporting of transfusion reactions at our center, 5 times increase in transfusion reaction and 2 times in donor reaction reporting along with improved documentation standards. Increased knowledge of haemovigilance among physicians and nurses can lead to improved transfusion safety.

A009

Whole Blood donor deferral vs Platelet donor deferral: An analysis towards expanding the potential donor pool

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Aim: To evaluate the patterns of whole blood donor deferral and platelet donor deferral and apply the relevant findings in order to convert deferred platelet donors for whole blood donation.

Method: Data of whole blood donors (WBD) and platelet donors (PD) presenting for donation were analyzed retrospectively over a period of 16 months, from September 2018 to December 2019, at a private hospital based blood bank in South India. The data was also reviewed to prevent the loss of platelet donors who are potentially fit for blood donation.

Results: It was found that total donors registered were 6353 for whole blood and 2695 for platelet donation. The deferred were 412 (6.5%) and 1376 (51%) for WBD and PD respectively. Among PDs, all (100%) the deferred were male donors with 1105(80%) of them deferred only due to non-suitable veins for platelet collection.

Conclusion: The study concludes that there is a potential loss of blood donors who are deferred for platelet donation. Efforts have to be made to motivate the deferred donors to convert them from platelet donation to whole blood donation in order to maintain adequate donor pool of WBD.

A010

Blood at my fingertips

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Aim: The RAH Trauma Service implemented a remote access blood fridge to provide immediate access to blood products during critical bleed incidents. The pilot study was conducted with O neg red cells to

- Resolve technical problems
  - Assess risk from both patient and product perspective
  - Demonstrate traceability of blood products
  - Determine feasibility of expanding inventory
  - Assess education and training processes

Method: A Memorandum of Understanding(MoU) between; Blood Organ and Tissue Programs(BOT), SA Pharmacy(RAH), Trauma Services RAH and the SA Pathology Blood Bank(BB) was developed along with governance framework. Educational resources were developed and implemented.

BloodSafe, RAH Trauma team and BB conducted

- reviews of reported incidents/near misses
- assessments of feedback from weekly case audits
- follow up for noncompliance
- reviews of Intec data

Results: The use of Intec and the BD Pyxis ADC linked to the blood fridge provided multiple advantages; traceability of the product and the staff; real-time monitoring of temperature control and alarms; supported compliance with required standards and guidelines[1,2,3] and a 'self-auditing process' for temperature control and replacement of products removed.

Human error or deviation from process was the most common issue identified. Staff frequently forgot to notify the BB products had been issued. On occasion blood products were dispensed to a room, rendering the product untraceable to a patient. The BD Pyxis system was set up to generate a report 3 times a day which allowed BB to identify these events and follow up in a time efficient manner.

Conclusion: We report on the successful introduction of a blood fridge for 'point of care' access in the Emergency department. Some issues remain regarding notification and allocation of blood products from the fridge. Interdepartmental efforts are currently underway to rectify these issues which will hopefully pave the way to an expanded inventory in the fridge.

A011

COVID Safe Critical Bleed Transport at RAH

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Aim: During the COVID–19 pandemic it became evident the Royal Adelaide Hospital (RAH) Massive Transfusion Protocol (MTP) shipper in use at the RAH (constructed with fabric materials) was identified as a potential cross-contamination risk due to the inability to clean and sanitise all the surfaces.

The RAH implemented the use of wipeable corflute shippers for MTP transport to minimise the risk of contamination for laboratory staff and clinical areas in the hospital. RAH implemented and reviewed the corflute shippers to assess feasibility for ongoing use.

Method: The SA BloodMove program had previously developed and implemented the locally manufactured corflute shipper for MTP packs for private organisation. Fifty (50) MTP corflute shippers were funded by SA Blood, Organ and Tissue Program. Instructional stickers were printed for packing configuration, a video instruction and other resources were produced and circulated.

Concern regarding the corflute shipper's ability to remain robust with frequent use in a busy trauma hospital was recognised. Due to SA's low infection rate the corflute shippers were only implemented if there was a known positive COVID -19 patient within the facility.

Feedback from laboratory staff and clinicians is sought on an ongoing basis.

Results: The corflute shippers continue to be implemented for all MTP transport across RAH effective immediately on notification of a positive COVID-19 admission to the facility. Due to SA's low infection rate there is limited feedback, however the shippers are reported to be awkward to use for both transport and packing in comparison with the original shippers but the ability to wipe and sanitise the surfaces of the shipper is recognised as a high priority for staff and patients by both laboratory and clinical staff.

Conclusion: The original shipper is favoured by staff for packing, visibility and transport ease but the potential infection risk concerns all staff. The robustness of the corflute shipper still requires ongoing testing.
Another option requires investigation for the future.

A012

I can see clearly

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Aim: There was recognition of the potential risk of transmission of COVID-19 from returned unused blood products for laboratory staff and clinical areas across the hospital. The RAH piloted the implementation of clear sealable plastic bags for transport of fresh blood products with the aim to assess usability for both clinical and Blood Bank staff, confirm clarity of the information on the attached sticker and assess any unforeseen issues with the change in practice.

Method: SA Pathology procured clear plastic bags. The South Australian BloodSafe team, in partnership with SA Blood Organ Tissue and BloodSafe eLearning Australia, designed and printed a sticker providing clear and concise instructions for checking by staff which was placed in the top left corner of the bag so as not to obscure any details of the blood pack or labels. Local BloodSafe nurses provided education and resources to clinical staff and the bags were implemented on July 1st, 2020 with an intended 1-month pilot followed by a request for feedback via online survey. Consideration for state-wide roll out would then be considered.

On the 17th of July, due to the Victorian escalation of COVID-19 cases, assessment of the pilot was brought forward. 132 Blood Link Nurses were emailed requesting feedback.

Results: The Survey Monkey received 28 responses pertaining to 81 receipts of blood products using the new system.

- 78% found the system user friendly
  - 96% confirmed the message on the sticker was clear
  - Any unforeseen issues such as packing method, was spontaneously addressed within 3 working days of commencing pilot and there were no further issues.

Conclusion: State-wide roll out of the clear sealable plastic bag is currently being undertaken. Sourcing of resources has caused minor delay.

A013

Clinical features and outcomes of major trauma patients who received out-of-hospital red cell transfusions prior to admission to The Royal Melbourne Hospital.

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Aim: Since 2011, The Royal Melbourne Hospital (RMH) Transfusion Laboratory and Ambulance Victoria have successfully implemented an out-of-hospital red cell concentrate (RCC) transfusion protocol. Previous audits showed the RCC "cold chain" integrity was maintained with zero wastage. This project aimed to retrospectively analyse the outcomes of RMH patients who received out-of-hospital RCC transfusions using the Victorian State Trauma Outcomes Registry (VSTORM).

Method: Adult patients with major traumatic injuries who received out-of-hospital RCC transfusions by Ambulance Victoria prior to arriving at RMH were identified from the RMH and VSTORM. Additional information was obtained by manual review of Ambulance Victoria and Transfusion Laboratory records.

Results: From April 2011 to December 2019, 80 patients (52 males, 28 females) received out-of-hospital RCCs prior to their RMH admissions. The median age was 41.5 years old (range 18 to 89). Seventy-one patients (89%) were involved in motor vehicle crashes, of whom 2 were pregnant and 7 were pedestrians at the time of injury. Forty-four patients (55%) were transferred from regional Victoria. Their median Injury Severity Score (ISS) was 33 (range from 4 to 66). Sixty patients were intubated prior to their arrival. The median number of RCCs transfused was 3 (range 1 to 8 units) with 30 patients, 1 patient and 1 patient receiving 4, 5 and 8 RCCs respectively. No transfusion reactions were reported. Twenty-five patients died in hospital and 47 patients were transferred to another hospital or rehabilitation facility.

Conclusion: Patients with differing traumatic injuries have had out-of-hospital RCC transfusions without known complications. The majority of injuries were from motor vehicle crashes, and over half were from regional Victoria. Further analysis using propensity score matching is underway to determine the impact of out-of-hospital RCC transfusions.

A014

Reduced volume blood prime for paediatric red cell exchange - a case study

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Red cell exchange (RCE) transfusion is an important therapeutic intervention for sickle cell disease. A procedural consideration in small children is the extracorporeal circuit volume (ECV) and potential for haemodynamic instability or acute anaemia during the procedure, or the possibility of priming fluid affecting the end haematocrit.
A blood prime is recommended if the ECV exceeds 10-15% of the patient's blood volume. The ECV of the Spectra Optia Apheresis system is 141-185mL, a greater volume is recommended to ensure blood has completely filled the set. We noted the return line was dark red in colour to the waste bag after priming with 150mL of RBC. Limiting the blood prime to this volume allows the remainder of the RBC unit to be used for the procedure, minimising wastage.

Aim: To review the effect of a 'partial blood prime' on RCE outcomes in a paediatric sickle cell patient undergoing RCE

Method: Retrospective audit of RCE performed for a paediatric patient with sickle cell disease in whom the ECV exceeded 10%, and a 150mL blood prime was used. Parameters reviewed include: haemodynamic instability, pre- and post-procedure haematocrit and fraction of cells remaining (FCR).

Results: Our patient was eight years old, with weight 22.5-24.6 kilograms. He underwent eight RCE procedures, using a Spectra Optia Apheresis system. The ECV was 10-11% of the patient's total blood volume. No adverse events occurred. Post RCE haematocrits were within 0.02 of the predicted haematocrit. The actual to calculated FCR was acceptable (0.82-1.05).

Conclusion: Use of a reduced volume blood prime did not detrimentally effect patient safety or accuracy or efficiency of the RCE. If the volume of donor red cells required to prime the circuit can be safely minimised, efficiency of RCE can be enhanced. Further consideration of the ideal volume for the blood prime may improve efficiency and enhance patient blood management.

A015

Weak D resulting from RHD exon 3 duplication initially reported in India also detected in unresolved weak D phenotypes in Australia

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Background and Aim: Accurate blood group typing for the clinically significant RhD antigen is important for blood donors, patients, and pregnant women. Approximately 0.2 to 1.0% of Caucasians carry *RHD* variants that type serologically as weak D. A recent report indicated that a weak D phenotype in the Indian population arises from a duplication of RHD exon 3, *RHD* exon 3 duplication (*RHD*Ex3dup)* allele. We reviewed a panel of samples with inconclusive RhD typing results to investigate whether this arose from such a duplication.

Method: Study comprised 36 unresolved weak D samples and 23 control samples. Samples were genotyped using BeadChip and by targeted blood group MPS exome sequencing (MiSeq Illumina). To confirm the presence of a suspected exon duplication, gel-PCR targeting *RHD*Ex3dup* allele breakpoint as well as high-resolution melting (HRM) assays targeting *RHD* exon 3 were used. A panel of anti-D monoclonal antibodies was used to characterise D antigen expression on RBC for a putative exon 3 duplication sample.

Results: The *RHD*Ex3dup* allele was detected in 69% (25/36) unresolved weak D samples using the Gel-PCR assay. The *RHD*Ex3dup* allele was not detected in the controls. Copy number variation based on MPS analysis was not definitive in predicting the presence of *RHD* exon 3 duplication and HRM was required to confirm exon 3 copy number. Serology demonstrated one example of RBCs encoded by *RHD*Ex3dup* lacked epitopes 1.2, 8.2 and 9.1 suggesting partial D expression when the duplication occurs.

Conclusion: We found examples of the *RHD*Ex3dup* allele in the Australian population for the first time and provide evidence that individuals with this variant have a partial D phenotype. Correct identification and characterisation of new *RHD* alleles encoding weak partial D is essential for appropriate transfusion and pregnancy management.

A016

Moving targets: Patient characteristics and locations of massive transfusions within a multi-site health network

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Aim: Management of massive transfusions (MT) requires seamless interaction between multiple parties across clinical disciplines and areas. This audit of 50 massive transfusion protocol (MTP) activations describes the patient, clinical and location characteristics across the five networked sites of Monash Health from March 2017 to May 2019. The audit reflects current practice prior to implementation of an updated MTP and electronic medical record (EMR).

Method: Retrospective audit of MTPs via transfusion laboratory records. Data collected included patient demographics, pre-existing bleeding risk, lead clinician, location(s), management, product use, patient outcome and MTP documentation compliance.

Results: 13/49 were triggered at sites outside the primary hospital, (one unclear/unavailable). Recipients were 58% female with median age 58 years [range 15-78]. 67% were managed by surgical units, including cardiothoracics (28%), GI surgery (16%) and obstetrics (12%). 38% had a pre-existing risk factor(s) for bleeding, typically anticoagulant or antiplatelet medications. Location changed at least once during 48% of MTPs, most commonly to operating theatre, intensive care or interventional radiology. Mean number of total units transfused was 21, (7.8 RBC, 4.6 FFP, 1.9 Platelets, 6.9 Cryoprecipitate). A single patient received 82 units of total blood products. 20% (10/50) of patients died during the hospital admission.

Complete MTP documentation was suboptimal: lead clinician's name and contact (present in 53%), notification of on-call haematologist by the registrar (present in 12%). Communication by the lead clinician deactivating the MTP (present in 18%).

Conclusion: MTPs frequently involve changes in patient location and handover between teams. Improved communication between the transfusion laboratory, clinical haematology staff and treating team(s) is essential for optimal patient outcomes. Documenting these gaps improves understanding of the processes involved and enables monitoring of progress following implementation of the redesigned MTP and introduction of an EMR.

A017

Pre-laboratory haematology registrars feel poorly equipped to cover transfusion medicine after hours without specific training

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AIM: To determine the level of experience, training and self-assessed knowledge of transfusion medicine (TM) among the Victorian pre-laboratory haematology registrars responsible for the transfusion laboratory after hours.

METHOD: A survey was emailed to Victorian pre-laboratory registrars in their first or second clinical year across three hospital networks. Those invited have, or previously had transfusion laboratory on-call duties. Responses were pooled and averaged.

RESULTS: The response rate was 92%, [11/12 respondents with an average 12 months' clinical experience]. Registrars estimated that transfusion medicine represents 18% of after-hours calls. Massive transfusions and clinical advice were most common, followed by (in decreasing frequency) transfusion reactions, permission to dispense restricted products and serology questions. The proportion of transfusion calls routinely escalated to consultants varied significantly by trainee [range 5-100%, mean 51%]. The proportion of calls that, with hindsight, should have been escalated to a haematologist was similar (54%).

Respondents recalled receiving zero (27%) or less than two hours (45%) of transfusion teaching prior to assuming on call responsibilities. No trainees had previous exposure to a transfusion laboratory environment. 91% of trainees self-rated their knowledge as 'Poor' or 'Very Poor'. 27% felt that ward-based medicine had 'not at all' prepared them for transfusion problems, with 72% feeling only 'somewhat' prepared. Most (82%) considered on-call TM exposure as valuable or very valuable to their training. 63% somewhat or completely agreed that "after-hours transfusion problems should be directed to laboratory haematology registrars". No respondents disagreed.

CONCLUSION: Without dedicated teaching, pre-laboratory trainees report poor knowledge and feel ill-equipped to answer TM questions. Exposure to this field is valued by clinical registrars, however most respondents indicated these issues would be better directed to laboratory trainees. This survey highlights an important educational opportunity for clinical trainees, even after 12 months' ward experience.

A018

The Australian Aplastic Anaemia and other Related Bone Marrow Diseases Registry (AAR) – blood product use in the idiopathic aplastic anaemia (iAA) cohort

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Aim: Idiopathic aplastic anaemia (iAA) is an uncommon bone marrow failure (BMF) disorder with a frequent requirement for red blood cell or platelet support regardless of treatment strategy employed. The AAR aims to capture all Australian patients with BMF including determining blood product usage.

Method: Analysis of national AAR dataset to examine blood product use in the iAA cohort.

Results: 130 of 156 evaluable patients with iAA had transfusion data available. Blood products were dispensed between March 2013 and October 2020. 10 patients had non-severe iAA and received neither red blood cells (RBC) nor platelets. 1 patient received RBC alone and 3 patients received platelets alone. The remaining 116 patients received both RBC and platelets, with a total of 4250 units of RBC and 4829 platelets administered. Of the transfused patients, median number of RBC dispensed was 17 units (range 1-322) and platelets 21 units (range 1-577). Of the 68 patients who achieved transfusion independence, median time from diagnosis until transfusion independence was 160 days (range 9-1681) with 37/68 (54%) achieving platelet independence prior to RBC independence. 49% of the 4829 units of platelets administered were apheresis platelets. 90/117 (77%) patients who received RBC received exclusively irradiated red cells. 33/130 (25%) of patients have died, and 27/33 (82%) received RBC or platelets within one week of death, including 6 patients who received blood products on the day of death.

Conclusion: Most patients with iAA require substantial RBC and/or platelet support. Many patients received blood products close to time of death, likely reflecting the acute nature of patients' terminal illnesses and the difficult clinical decisions at all stages of this disease. Ongoing examination of national practices documented in the AAR is crucial to inform optimal blood management strategies for this patient group.

A019

Evaluating a mitigation strategy to prevent incompatible blood transfusions due to wrong blood in tube

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Aim: The process of specimen collection and labelling has remained largely unchanged until the introduction of electronic medical records and an electronic pathology system in South Australia. The new sample labelling workflow introduced several additional steps for clinicians which increased the risk of errors including wrong blood in tube.

The primary aim was to research the cost implications of a compulsory, second pre-transfusion sample for patients without a transfusion history in the laboratory, the risk mitigation strategy used to reduce incompatible transfusions due to wrong blood in tube utilised by the British Society of Haematology.

Method: Data Blood Group and Antibody Screen sample data between 1st January and 31st December 2018 was compared with the number of patients who did not have a documented history within the pathology system. The approximate cost associated with implementing a second Blood Group sample for the patient group was calculated.

Results: A total of 39,579 ABO and RhD Blood Group and Antibody Screens were requested on the Pathology database between 1st January 2018 and 31st December 2018.

15,487 / 39,579 (**39.2%)** of requests were comprised of completed pre-transfusion testing for patients with no prior history.
The costs calculated included equipment for collection and charges associated with testing each sample. The additional costs of $15.98 per second test multiplied by 15,487 equates to $247,482. Clinician's time is not included, nor are costs associated with delays to patient care or discharges as a result of increased length of stay.

Conclusion: Unfortunately, it was determined at the time, such changes to clinical workload would increase the cost burden on the Health Network and Blood Bank thus was deemed to be prohibitive to progress.

A020

Label Before You Leave

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Aim: Implementation of an interface between the laboratory information system and the hospital EMR provided increased visibility of wrong blood in tube (WBIT) events. A working group was established with the aim of

- identify & understand contributing factors
  - assess risk to patients
  - identifying strategies to mitigate the risks including human factors to reduce labelling errors.

Method: The working group conducted environmental and clinical workflow mapping, developed reporting algorithms for improved data extraction, reviewed and updated electronic medical records education, approached clinicians across the network for feedback and observational audits were also conducted. BloodSafe implemented a WBIT reflection tool.

Results: The observational audits undertaken, indicated a lack of awareness and importance placed on positive patient identification throughout the sample labelling process. The system and processes from the interface implementation were intricate and complex. An education campaign was identified as the best starting point to re-educate clinicians about safe sample labelling practices.

A back to basics approach, incorporating a short slogan to promote patient identification and the safe sample labelling practice at the bedside was undertaken.
'Label Before You Leave' was the slogan decided upon. NHS UK Blood and Transplant provided permission to adapt their patient identification campaign to suit the local health network's needs. Posters were circulated to all clinical areas and screen saver images now appear on SA Health computers across the state.

Conclusion: The 'Label Before You Leave' campaign has been a successful first step to resolve the human factors and interrupted workflows contributing to sample labelling errors. The message will continue to be promoted to medical and nursing staff and students across SA to highlight the importance of confirming patient identification, and safe sample labelling at the bedside.

A021

Status of massive transfusion protocol - audit of massive transfusion protocol activations at a tertiary level hospital

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Aim: Haemostatic resuscitation has been advocated as the optimal practice for massive transfusion (MT) and has been integrated at most centres through the use of massive transfusion protocols (MTP). The aim of the study is to determine the utility of MTP packs and the use of thromboelastometry (TEM) in patients where MTP was activated.

Methods: All consecutive MTP activations with complete MTP packs at Flinders Medical Centre between 2018 and 2020 were reviewed. The first MTP pack consists of five red cells (RC), 4 fresh frozen plasma (FFP), and 1 platelet. Cryoprecipitate was included in the second pack on request. Data collected included number of activations resulting in unused, partially used or completely used MTP packs, use of thromboelastometry during activations.

Results: A total of 465 MTP activations, 393 activations using a single MTP pack and 72 using 2 or more packs were included in the analysis. MTP activations resulted in 53 (13.5%) fully used, 119 (30.3%) non-used and 221 (56.0%) partially used MT packs. Overall, 65.4% (1276/1952) of RC, 73.9% (1114/1508) of FFP, 68.9% (266/386) of platelets were transfused. Of the 221 partially used packs, 62.2% (681/1095) of RC, 76.3% (639/838) of FFP, 68.7% (147/214) of platelets were transfused. Nearly half (47.2%) of the MTP activations (185/392) had at least one ROTEM test performed, with the collection of the sample ranging from prior, during and up to 24hrs after the initial MTP activation.

Conclusion: Partially used MTP packs were common. Although unused MT packs signify futility, unused and partially used MTP packs should be assessed in context of ROTEM where ROTEM results may prevent unnecessary blood product transfusion.

A022

Trends in blood and blood product use during intraoperative orthotopic liver transplantation in South Australia's liver transplant centre

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Aim: Various strategies, technological advancements and introduction of viscoelastic assays have been utilised in orthotopic liver transplantation (OLT), which have contributed to the decline in allogeneic blood product use. The aim of the study was to examine the trends of blood and blood product use intraoperatively in orthotopic liver transplant (OLT) patients between 2003 and 2020.

Method: A retrospective analysis was performed on data extracted from the liver transplant database, comprising of patients who underwent OLT between 2003 and 2020 at Flinders Medical Centre. OLT patient demographics and morbidity details were extracted from the hospital database and blood product use from the Laboratory Information System. The study period was divided into three groups: 2003-2010, 2011-2015 and 2016 to 2020. Thromboelastometry (ROTEM) was implemented in our institution in 2011.

Results: A total of 346 OLT admissions, 135 in 2003-2010, 101 in 2011-2015 and 110 in 2016 to 2020 groups were included. The following table summarises the transfusion rates of red cells (RC), fresh frozen plasma (FFP), platelets (PLT) and cryoprecipitate (CRYO) including the median (interquartile range [IQR]) units of RC and other blood products transfused.

Blood and Blood products	2003-2010	2011-2015	2016-2020	p-value
RC	116/135 (85.9%)	78/101 (77.2%)	72/110 (65.5%)	0.001
FFP	115/135 (85.2%)	55/101 (54.5%)	17/110 (15.5%)	<0.001
PLT	84/135 (62.2%)	74/101 (73.3%)	64/110 (58.2%)	0.06
CRYO	54/135 (40.0%)	84/101 (83.2%)	72/110 (65.5%)	<0.001
RC (Units)	5 (4-9)	4(2-7)	3(1-6)	<0.001
FFP (Units)	5 (2.5-6.5)	5(3-8)	4(2-8)	<0.001
PLT (Units)	1(1-1.8)	2(1-2)	2(1-3)	0.03
CRYO (Doses)	2 (2-2.5)	3.5 (2-4)	2(2-4)	<0.001

Conclusion: There has been a significant change in transfusion rates and volumes of blood and blood products over the three study periods. Although not analysed, ROTEM may have played a significant role in these changes.

A023

Transfusion support for Australian sickle cell disease patients in the Australian Haemoglobinopathy Registry

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Aim: To describe red blood cell (RBC) transfusion support for sickle cell disease (SCD) patients in Australia using the Australian Haemoglobinopathy Registry (HbR).

Method: Analysis of HbR data for 314 SCD patients from 10 Australian sites across five states. Registry inclusion criterion is the presence of a significant sickling disorder. HbR uses an opt-off consent model and participation is voluntary.

Results:

One third of patients were regularly transfused (17% paediatric [<18 years], 58% adult). For transfused patients, 61% received automated exchange transfusions (59% paediatric, 62% adult), 17% manual exchange (6.2% paediatric, 21.6% adult) and 22% received simple/'top-up' transfusion (34% paediatric, 16% adult).

Transfusions routinely occur in the outpatient setting at 4-6 week intervals, with 57% of adults receiving 6 or more RBC units at each episode. For transfused patients the median (IQR) number of RBCs transfused in the preceding 12 months was 43 (14, 68). Overall, 11% patients have RBC alloantibodies (7% paediatric, 17% adults), with >1 alloantibody present in 1.6% paediatric and 9.9% adult patients.

Conclusion:

In spite of significant advances in SCD management, many SCD patients continue to receive large volumes of RBC transfusions, placing them at risk of alloimmunisation, which remains common. Alloimmunisation was seen less frequently in children than adults, likely reflecting both differences in SCD management and transfusion support, including fewer transfusions and greater degree of routine prophylactic antigen-matching, for these patient groups. Alloantibodies add complexity to cross-matching procedures for busy transfusion laboratory staff, and increase demand on phenotyped units.

These HbR data on current RBC requirements, utilisation of apheresis exchange transfusions and alloantibody frequency in the Australian context will be valuable for health service planning and for patient care.

A024

Deriving buffer ranges to guide Lifeblood donor management of full blood count results

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Aim: To improve the management of blood donors with full blood count (FBC) results outside of normal ranges and systematically reduce unnecessary external medical review.

Method: FBC ranges from direct-to-plasma donors donating between July 2018 to June 2019 were analysed. These donors were chosen to avoid potential confounders from prior blood donation. Data analysis occurred following the national implementation of the DxH 800 haematology analysers. In addition to reporting of the standard 95% reference intervals, 99.7% intervals (3 SD equivalent but non-parametric) were also analysed.
Buffer range results within 99.7% interval without other abnormal results were reported with advice not to undergo additional review. After implementation, an audit was conducted in NSW between April 1-15 2021. Initial estimation was this approach could prevent additional review of ~90% of donors with FBCs indicating abnormal values.

Results: Nationally 15710 results from new direct-to-plasma donors were used to determine reference range and buffer ranges. Donor Haemoglobin management remains unchanged to align with regulatory requirements. In a recent audit, 82% of donors with any abnormal FBC result had the abnormal value fall within these new buffer ranges.

Result	Buffer values
White blood cell count (WBC) ($\times 10^9$ /L)	< 60 years: 3.10 –13.90 ≥ 60 years: 3.10 –12.00
Neutrophils	< 60 years: 1.40 - 10.50 ≥ 60 years: 1.40 – 9.50
Lymphocytes	0.70 – 4.30
Monocytes	0 – 1.2
Eosinophils	0 – 1.3
RBC ($\times 10^{12}$ /L)	Males: 3.9 – 6.6 Females: 3.4 – 5.5
HCT (l/l)	Males: 0.36-0.54 Females: 0.32-0.51
MCV (fl)	79 - 102
MCH (pg)	21 – 35
RDW %	0 – 17.2

Conclusion: With the number of parameters measured in a FBC and using 95% reference intervals, ~50% of FBCs performed on blood donors return an abnormality prompting further medical review. Referring all donors with any abnormal value is excessive however guidance for management was not strongly evidence based. Analysis of FBC data from new direct-to-plasma donors provided specific guidance on where to set buffer ranges and determine donors who may have abnormalities that warrant further medical review. Since it is considered that blood donors are a general representation of the community these buffer values determined from ‘normal’ donors may be useful in patient populations, where additional follow up may be unnecessary in the absence of other specific clinical indication.

A025

Seroprevalence of SARS-CoV-2 in Australian blood donors

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Aim: When infections of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started to surge, Australian blood donor samples provided a valuable resource to help public health authorities map its spread. Looking for antibodies to SARS-CoV-2 is one way to estimate the true number of infections. Three Australian serosurveys have been conducted using anonymous samples that broadly reflect the community, including blood donor samples. These serosurveys aimed to understand the prevalence of SARS-CoV-2 antibodies at different times during the epidemic.

Method: Surveys 1 and 2 aimed to provide SARS-CoV-2 seroprevalence estimates in Sydney (April-June 2020) and nationally (June-Aug 2020), after the first epidemic wave. Survey 3 was conducted in Melbourne (Nov-Dec 2020) and aimed to measure SARS-CoV-2 seroprevalence following the state's second epidemic wave.

For the Sydney study, antibody testing was performed using an in-house SARS-CoV-2 immunofluorescence assay (IFA). IgG positive specimens were tested using IFAs for IgA and IgM, and a microneutralisation assay. For the national and Melbourne surveys testing was performed using the Wantai SARS-CoV-2 total antibody ELISA with secondary testing of positives by IFA (IgG, IgM and IgA) and microneutralisation assay.

Results: Of the 1548 blood donor samples included in the Sydney serosurvey, 12 (0.8%) tested positive for IgG. These samples were negative for IgA and IgM and 11 (92%) had neutralising antibodies. IgG positive samples had low titres and the donors were also younger in age (20-29 years). The national (n = 3213) and Melbourne samples (n = 4800) are being analysed.

Conclusion: The available seroprevalence estimate for Sydney indicated limited community transmission of SARS-CoV-2. Testing residual blood from donors has provided a pragmatic approach to conducting large-scale serosurveys during the SARS-CoV-2 pandemic. Serological surveillance data can help inform public health responses and provide useful baseline information for local health authorities to monitor vaccine effectiveness into the future.

No conflict of interest to disclose
Australian governments fund Australian Red Cross Lifeblood to provide blood, blood products and services to the Australian community
The Sydney serosurvey results were published at the time of abstract submission (Gidding HF et al, Seroprevalence of SARS-CoV-2-specific antibodies in Sydney, Australia following the first epidemic wave in 2020, Medical Journal of Australia, 2020).

A026

Platelet Wastage in The Sutherland Hospital: an audit.

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Aim: The aim of this audit was to identify causative factors for platelet wastage in The Sutherland Hospital to guide future waste reduction strategies.

Method: A total of 36 discarded units of platelets from Sutherland Hospital from January 2018 to October 2019 were identified for analysis. Data from electronic records was analysed to identify relevant clinical variables including initial platelet count, diagnosis, clinical indication for platelets and reason for discard. These variables were then descriptively analysed to identify where platelet wastage occurs most frequently and common causative factors.

Results: The largest area of platelet wastage identified was in the peri-procedural setting, representing 22/35 (63%) of cases. This was followed by treatment of major bleeding (9/35, 26%) and severe thrombocytopenia (4/35, 11%). Of platelet orders that could be assessed by National Blood Authority Patient Blood Management Guidelines, 43% (10/23) were considered inappropriate, while 13% (3/23) were considered usually inappropriate and the remaining 43% (10/23) considered appropriate.

The major cause for platelet wastage was failure to stand down platelets when no longer clinically required, accounting for 25/35 (71%) of cases. Of these cases, 18/25 (72%) were peri-procedure, 5/25 (20%) were related to activation of the Massive Transfusion Protocol (MTP), 1/25 (4%) for bleeding without activation of MTP and 1/25 (4%) for severe thrombocytopenia. Other reasons for platelet wastage included logistical issues such as inter-hospital transfer and delayed procedures (7/35, 20%), duplicate platelet orders (2/35, 6%) and improper platelet handling (1/35, 3%).

These findings suggest that interventions targeting peri-procedural platelet waste as well as encouraging appropriate platelet prescribing may be most effective in our setting.

Conclusion: Platelet wastage at Sutherland Hospital occurs most frequently in the peri-procedural setting, largely due to failure to stand down platelets.

A027

Expedited access to fibrinogen concentrate during COVID-19 contingency planning

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Aim: Fibrinogen Concentrate (FC) is not currently available through national blood supply arrangements for use in acquired fibrinogen deficiency associated with critical bleeding. SA Health independently purchased FC as part of COVID-19 contingency planning. A limited amount of stock has subsequently been made available for clinical use. This project aimed to build system familiarity with the product, develop criteria for access and implement distribution, governance and data collection models.

Method: In August 2020, 336g of RiaSTAP® was released to a limited number of SA Health facilities under a pilot program to test models for access and supply. 202g has been retained as contingency stock. Local Health Networks (LHNs) endorsed clinical protocols/procedures through their respective Blood Management Committees. LHN governance and communication channels were put in place to ensure clinical areas and transfusion laboratories were aware of the availability of product and the criteria for use. Local protocols developed by clinicians included a threshold of FIBTEM levels ≤ 6 for use in critical bleeding where thromboelastometry testing is available. FC doses were allocated to hospitals in metropolitan LHNs, the retrieval service and selected hospitals in regional SA based on historical cryoprecipitate use. Rural hospitals without laboratories were allocated stock based on risk profiles (eg retrieval times and obstetric activity).

Results: A Critical Bleeding Advisory Group advises on implementation matters, monitors use, adverse events and clinical outcomes. LHNs are required to input utilisation and clinical outcomes data into a REDCap® database. Between August 2020 and April 2021, a total of 82 grams was utilised by 20 patients.

Conclusion: There is now confidence in the system ability to access limited FC supplies to supplement and complement cryoprecipitate use in the management of critical bleeding. The criteria for access will be reviewed considering the low utilisation rate.

A028

Serological Interference of Anti-CD47 Immunotherapy in Pre-Transfusion Testing: The Peter Mac Experience

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Introduction/Aim: CD47, a glycoprotein expressed on all human cells, binds to signal-regulatory protein α on macrophages triggering the inhibition of phagocytosis.[1] Magrolimab (Anti-CD47) is a human monoclonal Immunoglobulin G (IgG) subclass 4 antibody that blocks CD47 thereby targeting cells for destruction via macrophage phagocytosis. Plasma from patients receiving anti-CD47 immunotherapy have been shown to interfere with all pre-transfusion testing phases, interfering with ABO blood grouping, phenotyping, antibody screening and identification.
We report anti-CD47 interference in pretransfusion testing in one patient and evaluate mitigation strategies.

Study Design/Method: Samples from a patient on Magrolimab were tested for blood grouping, direct antiglobulin test (DAT), antibody identification with and without papainised cells, titration and carryover studies using column agglutination testing (CAT).
Indirect antiglobulin testing (IAT) with Rapid Antibody Medium (RAM) and without enhancement media (classic) were subsequently performed using tube techniques. Different AHG reagents (polyspecific anti-IgG-C3d, monoclonal anti-IgG with or without anti-IgG4) were used at IAT phase. Eluates were made using rapid acid elution.

Results: Panagglutination was observed in antibody screen and identification. There were no interferences when performing ABO forward typing. The patient was determined to be group O Positive. In addition, no carryover was noted, in spite of the anti-CD47 in the sample showing a very high titer (1: 8192 dilution).
Tube IAT results (with and without enhancement) and using 3 AHG reagents will be presented. The eluate reacted 3+ to 4+ with 11-cell panel by tube IAT using polyspecific anti-IgG-C3d and monoclonal anti-IgG. IAT was negative with a monoclonal anti-IgG not detecting IgG4.

Conclusions: Magrolimab immunotherapy reported here interfered with CAT. However, ABO forward typing using CAT was unaffected. In addition, no carryover was seen when using automated CAT.
As expected from previous reports, interference with IAT was dependent on the anti-IgG used. Monoclonal reagents without anti-IgG4 activity were helpful in mitigating the interference at AHG.

References:
Velliquette RM, et al. Monoclonal anti-CD47 interference in red cell and platelet testing. Transfusion 2019; 59; 730-773

Laser incubation of clinical samples for rapid antibody screening

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Aim: Pre-transfusion antibody screening and crossmatching, where the presence of IgG antibodies is detected in patient plasma, requires incubation of the sample at 37 °C. Laser-driven incubation has been developed as a new platform for rapid sample heating. We test laser heating technology on clinical samples for a range of blood group systems.

Method: We have tested over 94 patient plasma samples known to contain one or more antibodies (Table 1) from several key blood group systems. Using anti-IgG gel cards, plasma is mixed with reagent RBCs and is heated in the infrared (980nm) laser system for 1 to 5 minutes and compared to those heated in the dedicated gel card heating block for 5 minutes.

Antibodies	No. patients
D	33
C	12
c	7
Cw	4
E	19
Fya	5
Fyb	1
Jka	5
Jkb	1
K	5
Kpa	1
S	1
Total	**94**

Table 1. Antibodies tested

Antibody	Heating Block	Laser		
	5 mins	1 min	2 mins	3 mins
D	1	0	0	1
D	2	1	1	2
Cw	3	3		
E	4	4		
Fya	2	1	2	
Fya	3	3		
Fyb	1	+/-	1	

Table 2. Score (0 - 4 in gel card) for each antibody in heating block compared to laser

Results: Strong and weak antibodies were present across all blood group systems tested. Strong antibodies were detectable with only 1 minute of incubation by the laser. Very weak antibodies required up to 3 minutes incubation (Table 2). Difficulties with working with clinical samples have been overcome, particularly fibrin formation which produces false positives, caused by localised intensities of the laser light. Variation of the design of the laser optical input to prevent false positives will be presented.

Conclusion: Laser incubation technology for pre-transfusion antibody screening and cross matching is a viable alternative to slower heating methods. Infrared laser light can safely and rapidly heat patient plasma samples to detect the presence of weak antibodies within just a few minutes.

A030

Increased potassium leakage in red cells from donors with familial pseudohyperkalaemia

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Aim: Familial pseudohyperkalaemia (FP) is caused by polymorphisms in the *ABCB6* transporter gene, and whilst asymptomatic, causes increased potassium leakage from red cells (RBC) when refrigerated. Transfusion of these RBC to neonates could have serious implications. Blood donors with this condition have previously been identified in the UK but not in Australia. The aim of this study was to characterise stored and irradiated RBC components from blood donors with FP.

Method: During a research data review, 4/798 RBC with high levels of potassium leakage were identified. The four donors, together with two age- and sex-matched controls each, gave a whole blood donation following informed consent. RBC components were split into 6 paediatric packs. Two packs were not irradiated; two were gamma-irradiated on day 1 post-collection, and tested on day 2, 3, 7 and 15; and two were irradiated on day 14 and tested on day 15, 16, 21 and 28. Red cell indices, extracellular potassium and haemolysis were measured.

Results: DNA analysis confirmed the FP status of all four donors. RBC from FP donors had significantly higher potassium release during storage compared to RBC from controls (p=0.01). The potassium concentration in FP RBC irradiated on day 1 was not significantly higher than controls (p=0.223), whereas potassium concentration in FP RBC irradiated on day 14 was initially higher but equalised during storage (p=0.01). Unexpectedly, haemolysis was slightly higher in RBC from control donors (p=0.033). There was a trend towards a lower MCHC in FP RBC towards the end of storage, but the overall difference was not significant (p=0.078). No other differences were observed.

Conclusion: Potassium release is higher in FP red cells, but not further exacerbated by irradiation. Determining the prevalence of FP in Australian blood donors will enable an understanding of the true clinical risk posed by these donations.

A031

Phage display reveals anti-D antibody variable gene usage is not limited to the VH3-33 "superspecies" for anti-D donors in Australia

Ms Eunike McGowan[1,2,3], *Prof Robert Flower*[1,2,4], *Prof Catherine Hyland*[1,2,4], *Dr Martina Jones*[2,3], *Prof Stephen Mahler*[2,3], *Dr Xuan Bui*[1,2,3]
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Aim: Manufacturing RhD-immunoglobulin (RhIg) is reliant on a plasma supply from donors with anti-D antibodies. Anti-D monoclonal antibodies (mAbs) have been considered an attractive alternative to RhIg. Assessment of these anti-D mAbs in relation to its efficacy in preventing anti-D alloimmunisation remains ongoing. Previous studies revealed that anti-D antibodies commonly have a κ light chain and preferentially use the variable heavy (VH) 3-33 "superspecies" germline alleles. We have reported an example of this for a newly immunised anti-D donor in Australia. We aimed to identify the anti-D antibody germline V-gene usage for a long-term anti-D donor who has participated in the Rh program for over 50 years.

Method: Whole blood from a retired anti-D donor was obtained for immune human antibody phage display library construction. After red blood cell (RBCs) biopanning, anti-D clones were isolated and reformatted to human IgG1 molecules for flow cytometry and serological testing to confirm RhD specificity. ImMunoGeneTics (IMGT) -V-QUEST was used to identify V-gene usage.

Results: Library construction, RBC biopanning and antibody reformatting resulted in the development of 2 anti-D mAbs, referred to as "2-11" and "2-12". These mAbs were confirmed to react with D-positive but not with D-negative RBCs. For both mAbs, IMGT analysis showed the VH gene usage were the same: *IGHV* 1-46*01, *IGHD* 6-13*01 and *IGHJ* 6*02. The mAbs had a κ light chain and the gene usage differed between clones 2-11 (*IGKV* 1-12*01; *IGKJ* 3*01) and 2-12 (*IGKV* 1-8*01; *IGKJ* 4*01).

Conclusion: This study identified the retired donor has anti-D antibodies with a κ light chain but not with usage of VH3-33 "superspecies". This shows that there may be additional diversity in the donor's polyclonal anti-D antibodies that have contributed to the Australian RhIg supply. This finding suggests that a mAb blend may be required to mimic properties of polyclonal RhIg.

A032

Transient antibodies resembling "anti-LW" may be a precursor in the production of anti-D antibodies: An anti-D donor case study

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Aim: RhD-immunoglobulin supply is maintained by volunteer D-negative donors, most of whom have been deliberately immunised to produce anti-D antibodies. Recently, a monoclonal antibody (mAb) clone "PR3-3" isolated from a phage display library derived from a newly immunised anti-D donor, was found to initially appear as "anti-LW". Transient antibodies *resembling* anti-LW have been hypothesised as "an antecedent in the immune response leading to the production of anti-D" [1]. This study aims to investigate the PR3-3 mAb specificity.

Method: Anti-D donor RBCs underwent direct antiglobulin testing (DAT) on 3 occasions. To investigate PR3-3 mAb specificity to LW, the mAb was tested against a RBC panel and against ExpiCHO cells expressing a recombinant LW protein using flow cytometry and/or serology. With Clustal Omega, an amino acid sequence alignment of the antibody V-region encoding the PR3-3 mAb with 3 other phage-derived anti-D mAbs from the same donor was analysed.

Results: A transient autoantibody was detected when the donor's RBCs were 1+ DAT positive on the 1st and 2nd occasion and negative on the 3rd occasion. RBC testing showed the PR3-3 mAb was not specific to LW, primarily by its strong reactivity to a RBC sample with a D-positive, LW(a-b-) phenotype and appearance as anti-D upon tube titration. There was also a lack of PR3-3 mAb reactivity to ExpiCHO cells expressing recombinant human LW protein. The alignment showed there was 94.1% V-region similarity between the PR3-3 mAb and 3 anti-D mAbs from the same donor.

Conclusion: This study provided evidence that transient autoantibodies *resembling* "anti-LW" may be a precursor in the mutation process leading to affinity matured anti-D antibodies. This may explain the presence of a transient autoantibody and the high level of V-region sequence similarity between the PR3-3 mAb and 3 other anti-D mAbs. Further study into the structure recognised by the PR3-3 mAb remains ongoing.

Reference:
[1] G. Daniels. Human Blood Groups, Place Published: Wiley-Blackwell; 2013.

A033

Sustained reduction in Wrong Blood in Tube (WBIT) incidents at Townsville University Hospital (TUH)

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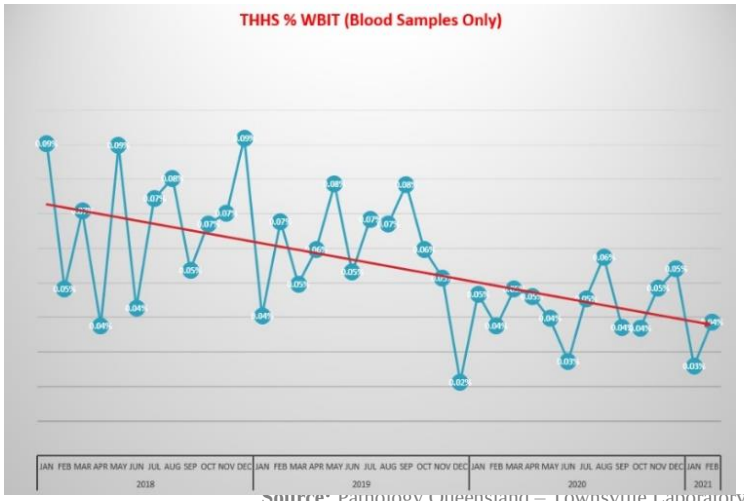
[1]*Queensland Health - Townsville Hospital Health Service, Douglas, Australia*

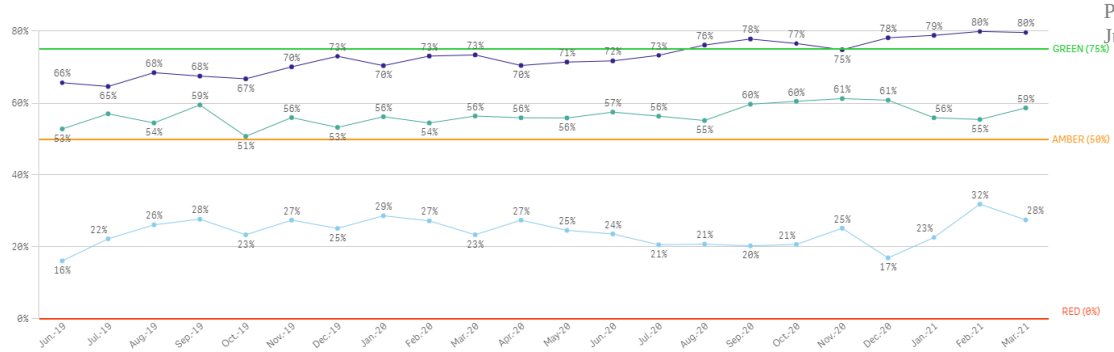
Aim: To achieve a sustained reduction in WBIT incidents at TUH using the positive patient identification (PPID) functionality within the integrated electronic Medical Record (ieMR), to reduce the risk of delayed treatment, adverse transfusion outcomes and unnecessary specimen recollection.

Method: TUH is a digital hospital, patients are provided with unique bar code identifiers on their armbands for accurate patient identification and added patient safety. Through local WBIT data collection and analysis, it was determined that overriding the scanning function in ieMR to confirm patient identification, pre-printing of specimen labels, and having an alternative patient's chart opened in ieMR were the primary reasons behind preanalytical errors. An electronic dashboard was developed to monitor compliance of PPID and positive accession identification (PAID).

Results: The dashboard provides enhanced visibility for clinicians and is the foundation to a consistent approach to improving best practice, making culture change achievable. The absolute number of WBIT incidents reduced from 187 in 2018, to 116 in 2020. There has been an observed reduction in misidentified patients, unnecessary phlebotomy, labour time savings and reduced processing time in pathology, and an improvement in the ability to measure compliance with best practice against performance, while maintaining and improving patient safety.



Source: Pathology Queensland – Townsville Laboratory



Source: ClinSite PPID Dashboard TUH Jun 19 – Mar 21

Conclusion: Ultimately, workplace culture is an influential factor in compliance with patient safety processes, therefore by using an organisation wide approach to monitoring through the PPID/PAID dashboard, managing, and reviewing WBIT discrepancies, the opportunity for error has reduced. A reduction in WBIT incidents will return valuable time to frontline clinicians and pathology staff, reduce the financial impact for specimen recollection, and improve the overall patient's healthcare journey and safety.
The concept behind this initiative is applicable to other functionalities within ieMR, such as medication administration, and can be applied to all digital health services to improve the provision of safety and quality to consumers.

A034

Rh haplotype prediction for Indigenous Australians from South-East Queensland

Miss Aoibhe Mulcahy[1], *Prof Robert Flower, A/Prof Catherine Hyland, Yew Wah Liew, Brett Wilson, Maree Perry, Tamika Campbell, Sudhir Jadhao, Dr Shivashankar Hiriyur Nagaraj*
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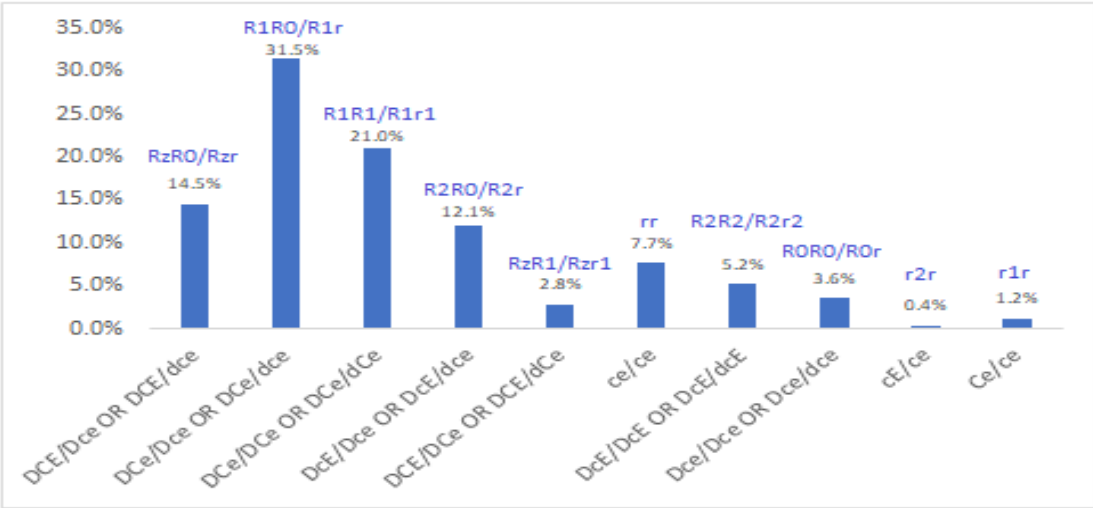
Aim: The RH blood group system is one of the most clinically significant blood group systems in immunohematology. However, sequencing the *RHD* gene remains extremely challenging due to its 93.8% homology with the *RHCE* gene, particularly in exons 8 and 10. Additionally, there is little transfusion research available specifically relating to the Indigenous Australian population. Here, we aim to identify the most frequent RH haplotype patterns found within the Indigenous Australians to improve the understanding and transfusion outcomes.

Method: We collaborated with the Carbal medical staff who collected 6mL EDTA blood samples with informed consent from each of the recruited 245 study participants under HREC approval. ABO and Rh serological typing were performed on all samples, and compared with a previous Western Desert Indigenous study from individuals of the Martu people

Results:

The 

most common Rh phenotype was D+C+c+E-e+ observed in 77 (31.5%) participants. The predicted haplotypes for these is either R1R0 or R1r depending on whether the *RHD* gene is homozygous or hemizygous. In contrast we found 3% of individuals in the Western Desert with this haplotype. R1R1 or R1r' was discovered at a frequency of 21%, which was higher than the 16% frequency found among Australian Indigenous individuals in the Western Desert. RzR0 or Rzr was expressed in 14.5% of South-East Queensland Indigenous Australians, which was lower than the 36% of Indigenous Australian individuals from the Western Desert.

Conclusion: Points of difference in the frequencies was identified between the South-East Queensland Indigenous Australians and the Western Desert Indigenous Australians. Expanding knowledge about the diversity of blood groups among the Indigenous people of South East Queensland using genomics data may contribute to appropriately matched blood for transfusion support. We want to sincerely thank all staff and research participants from the Carbal Medical Centre for collaborating on research to better understand the blood types of Indigenous Australians

A035

Establishing a Regional and Remote Apheresis service in Western NSW

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Aim: Traditionally patients requiring apheresis from regional and remote areas have been compelled to seek treatment at metropolitan hospitals, at great social and economic cost to the patient and the health service, or to receive apheresis in local ICU units using renal replacement therapy machines. We outline the methods we used to establish, finance, and run, an apheresis service in Western NSW.

Method: Discussion will include required infrastructure, staffing, training, governance, and illustrative patient cases, and how issues with starting a new service were overcome.

Results: Since commissioning in 2017, 27 patients with haematological, neurological, renal, and respiratory diseases have received 700 plasma exchanges. This has resulted in a major improvement in patient care, and substantial savings to patients and the health service.

Conclusion: Rural and regional areas are suitable locations for apheresis services provided they are adequately resourced.

A036

Congenital sideroblastic anaemia presenting antenatally as severe fetal anaemia

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Severe fetal anaemia of unknown aetiology can present a diagnostic challenge. Rare causes of fetal anaemia include congenital sideroblastic anaemia, a rare group of disorders that typically manifest during infancy and early childhood. In this case series, we describe three pregnancies complicated by congenital sideroblastic anaemia presenting antenatally in the same woman. Although the couple were known to be consanguineous, there was no family history of sideroblastic anaemia. The index case was a monochorionic diamniotic twin pregnancy in which both neonates presented with severe anaemia at birth and resulted in the neonatal death of one twin, whereas the two subsequent cases of severe fetal anaemia were detected during pregnancy and successfully managed with intrauterine blood transfusions (IUT). The three surviving children required several neonatal transfusions and were later diagnosed with congenital sideroblastic anaemia on bone marrow aspirate. To our knowledge, this is the first case series describing congenital sideroblastic anaemia presenting in the antenatal period with surviving patients and thereby highlights the importance of considering fetal anaemia early in pregnancy and the potential for early intervention with IUT to improve survival outcomes in this group of patients.

A037

Enhancing immunoglobulin access outside national blood arrangements using a web application

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Aim: To improve the efficiency of Jurisdictional Direct Order (JDO) requests and approval for access to Immunoglobulin (Ig) in Western Australia (WA) which fall outside the criteria for the clinical use of immunoglobulin in Australia (the Criteria).

Method: Analysis of web-based programmes identified REDCap™ as a suitable and secure platform for the JDO process. A JDO request and approval form was developed incorporating mandatory fields to capture patient and disease demographics, product type, dose and frequency, requestor details and clinical outcome data. Electronic approvals and email notifications were incorporated into the form to improve approval turnaround times. An option to generate standing orders was also included to streamline repeat requests.

Results: Following a successful pilot at a WA tertiary hospital, the web-based request and approval process was implemented state-wide in September 2020. Summary data is presented below.

Figure 1: Summary data

Condition	No. single doses	No. multiple doses	No. patients
Haemolytic disease of the newborn (HDN)	6		6
Vaccine induced prothrombotic immune thrombocytopenia	1		1
Inflammatory vasculitis		18	2
Statin-naive myositis		18	1
Inflammatory myositis	1	6	2
Interstitial lung disease	1		1
Autoimmune encephalitis	1		1
Haemolytic anaemia	1		1
Antibody deficiency	1		1
Other rare diseases	3		3
Total	**15**	**42**	**19**

Between September 2020 and April 2021, 19 patients received 10% Privigen. Actual body weight dosing ranged from 0.4g/kg to 2g/kg. All mandatory data fields were complete. Requests for HDN and for patients with repeated standing order requests were supported by clinical outcome data. Specialists in Immunology accounted for 32.5% of requests.

Conclusion: Transition to a web-based request and approval process has improved the quality and timeliness of JDO data. Monitoring trends and outcome data has proved simple, with summary data provided to the National Blood Authority to strengthen evidence for conditions to be included in future updates of the Criteria.

A038

Haemovigilance – beyond watching – acting on the data to help future management of patients

Mrs Carly Olsen, *Deborah Pinchon[1,2,3]*

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Background: National haemovigilance reporting requires approved health providers (AHP's) to submit numerical data including event type, severity, outcome, imputability score, product type, age and gender of patient and date and time of transfusion annually. This limited data set fails to provide adequate clinical detail to inform educational opportunities to improve patient care.

Aim: To demonstrate the benefits of requesting AHP's to provide additional clinical information on allergic type reactions within the WA Haemovigilance Program

Method:

AHP's were requested to submit additional clinical information including signs and symptoms of the reaction, investigations, treatments as well as product specifications for all reported allergic type reactions from 01 January to 30 June 2020.

Results:

Sixteen allergic type reactions were analysed. Seventy-five percent of reactions occurred in females and predominantly with the use of apheresis platelets. All patients experienced dermal symptoms associated with pruritis. Seventy-five percent of patients received some form of treatment for their symptoms, however there was wide variation in the types of treatments used. Sixty-two percent of patients had no investigations following the reaction, again with wide variation in the investigations undertaken. Overall 94% of reactions were associated with minor or no morbidity.

Fifty percent of cases were assessed with an imputability score of indeterminate, the mean number of symptoms reported in this subgroup was 3 and all received medication in treatment of the reaction.

Conclusion:
The additional clinical data and product specifications provided a unique insight into the variability in practice relating to the identification and management of allergic type reactions; this is consistent with findings from international haemovigilance systems. The WA Department of Health have implemented a range of targeted initiatives in response to the observed variations in practice, including: leading a 'Haemovigilance Masterclass', developing a 'Haemovigilance Quality Assurance Program' and making recommendations within the Annual Haemovigilance Report.

A039

Improving the management of iron deficiency in the emergency department.

Dr Jeremy Ong[1], *Ms Leanna Pickles[1], Ms Christine Akers[1], Ms Cristina Roman[1], Dr Nicholas Adams[1], Dr Susan Morgan[1]*
[1]Alfred Health, Melbourne, Australia

Patients with iron deficiency anaemia presenting to the emergency department (ED) are often inappropriately transfused.[1] In many cases, their iron deficiency is unrecognised or inadequately treated with iron supplementation.[2]

Aim: The aim of this study was to determine whether updating practice guidelines and streamlining the process for iron replacement can improve the management of iron deficiency in the ED.

Method: A retrospective audit was performed on iron deficient patients (serum ferritin ≤30mg/L) who presented to the ED of a tertiary hospital over a three-month period before and after implementing new practice guidelines for iron deficiency management. Patients admitted for inpatient care were excluded. The updated guidelines recommended testing for iron deficiency in patients receiving red cell transfusions, endorsed administration of intravenous iron in the ED and streamlined the process for outpatient iron infusions through governance by the haematology laboratory. The implementation also included staff education, written patient information and designing a framework for communication with patients and their general practitioners (GPs).

Results: There were 33 iron deficient patients managed by the ED before implementing the new guidelines, and 59 patients afterwards. Iron deficient patients appeared to receive more iron supplementation after the new guidelines were in place (31/59 53% versus 12/33 36%, *p=0.1191*). The improvement was primarily due to increased iron infusions (22/59 37% versus 2/33 6% *p=0.0012*). In patients who did not receive iron replacement, there was improved follow-up of the iron deficiency, primarily through direct communication from ED to GPs (16/28 57% versus 4/20 20% p=0.0112). Patients who presented with symptoms of iron deficiency were more likely to receive iron replacement compared to patients who presented with bleeding or when the iron deficiency was diagnosed incidentally. Two iron deficient patients (6%) received a red cell transfusion prior to implementation of the new guidelines (haemoglobin 56g/L and 75g/L), and 14 patients (24%) received a transfusion afterwards (median haemoglobin 65g/L, range 52 to 88g/L).

Conclusion: Management of iron deficiency can be improved in the ED by changing practice guidelines and increasing the access to intravenous iron infusions. Future strategies are required to minimise unnecessary red cell transfusions in iron deficient patients.

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2. Rohrig G, Klossok W, Becker I, et al. Prevalence of anemia among elderly patients in an emergency room setting. European Geriatric Medicine 2014;5:3-7

A040

Blood Product Utilization in a Paediatric Apheresis Service.

Dr Samantha Senavirathna[1], *Dr Anthea Greenway[1], Dr Amanda M Walker[1], Dr David Metz[1], Ms Anna Duncan[1], Ms Zoe Millard[1], Mr Brendan Cusack[1], Ms Anne Kinmonth[2], Ms Mary Commande[2], Dr Jacqueline Fleming[1]*

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Introduction: Therapeutic Apheresis involves separation of the components of whole blood to remove pathological components or to produce a therapeutic product. Transfusion support is commonly required, particularly in children where the volume of the Apheresis circuit can represent a significant proportion of the circulating blood volume. No published standards for blood product support exist, therefore there may be variation in practice according to institutional Standard Operating Procedures. Audit of blood product utilization can assist in efforts to reduce wastage and improve transfusion practices for children requiring Apheresis.

Aim: Objective of this study was to describe the blood product utilization for all apheresis procedures performed at the Royal Children's Hospital, Melbourne in 2020. This will provide baseline data will inform quality improvement activities aiming to reduced wastage and improve patient blood management.

Methodology: A retrospective audit of blood product usage across all Apheresis procedures performed Jan Dec 2020 was undertaken. Clinical data was collected on review of the medical record and documented in Excel 365.

Results: 41 individuals underwent 270 Apheresis procedures in 2020. 22 (53.66%) were male, 19 (46.34%) were females. Mean age of the population was 10.5 years (SD=5.35); mean weight was 41.72 kg (SD=22.81).

	Blood Product Ordered	Blood Products Used	Blood Products Discarded	Discard Rate	Pre procedure	Post procedure
Therapeutic Plasma Exchange	FFP 111	FFP 105	FFP 6	5.40%	0	7 Cryoprecipitate
Red cell exchange	LPFRBC 429 units	LPFRBC 409 units	LPFRBC 20 units	4.66%	0	0
Stem cell collection	LPFRBC 22 units	LPFRBC 22 units	0	0%	3 LPFRBC units 756 ml of platelets	1 red cell unit 1 platelet unit
CAR T collection	LPFRBC 24 units	LPFRBC 24 units	0	0%	2 LPFRBC units 295ml of platelets	1 platelet unit
ECP	LPFRBC 4 units	LPFRBC 3 units	LPFRBC 1 unit	25%	0	0

FFP= Fresh Frozen Plasma, LPFRBC= Leukocyte poor filtered packed red blood cells

Conclusion: Therapeutic Apheresis procedures require significant blood product usage particularly in children. Further investigation has suggested some practice changes to target reductions in wastage, with capacity to review this annually to ensure ongoing improvements in patient care.

A041

Blood Stock Management During the COVID-19 Pandemic at a Remote Blood Centre in Sri Lanka.

Dr Samantha Senavirathna[1]
[1]*National Blood Transfusion Service, Colombo, Sri Lanka*

Introduction: SARS-CoV-2 or COVID-19 has been a challenge in the medical field including blood banks. COVID-19 had a significant negative effect on blood collection in Sri Lanka. However, blood demand remained the same; therefore, in blood bank operations vigilant stock management and monitoring was essential to overcome the challenges. Batticaloa is a blood centre in Sri Lanka, which is located around 325km away from the capital city, Colombo. Here we present the way we managed the blood stocks during the pandemic.

Case Report: In 2019 there were 5384 donations at the regional blood centre, Batticaloa, Sri Lanka; however, due to COVID-19 pandemic and island wide lockdown it was dropped to 3948. Hence, actions were needed to manage the blood stocks.
Donor deferral criteria were introduced to minimize the risk of donor and staff exposure. Blood donation campaigns were arranged with practicing social distancing and with proper use of PPEs. Hence, it was possible for blood donors to be confident for blood donation. Social media campaigns were conducted to make the public aware about blood donation and government departments, forces and education institutes were informed to promote blood donation.
Patient Blood Management (PBM) was practiced optimizing medical and surgical patients. Furthermore, as Sri Lanka has a nationally coordinated transfusion service, it was possible to get blood products from the unaffected areas that had an optimal blood collection with proper communication.
However, family replacement donation was not practiced.

Conclusion: During the COVID-19 pandemic crisis, a multidisciplinary approach is needed for blood stock management. Collaborative activities with other organizations and the community would be helpful. Blood redistribution is an important measure. Such situations emphasize the importance of a nationally coordinated transfusion service.

A042

Mindfulness in blood bank practice

Dr Samantha Senavirathna[1]
[1]*The Royal Children's Hospital, Melbourne, Parkville, Australia*

Introduction: Simply, mindfulness is intentionally maintaining individual's attention to the present. Although it has a religious background, anyone can practice it formally, irrespective of the religious believes, with proper training or practice it informally in day-to-day life including the duty hours. Mindfulness has become popular in psychotherapy around the world and mindfulness programs have been introduced to many institutes, including health sector to improve quality.

Discussion: Human resource is a critical factor in quality control even in the presence of advanced automated systems. However, work related stress can influence the blood bank staff. Work related stress and burnouts can be managed with mindfulness. Furthermore, it positively affects the individual's physical and mental health and brings enthusiasm to work.

In blood bank practice, concentration to the work is important in every step to maintain the quality from vein to vein. It is undebatable that blood collection, sample handling, testing, results interpretation, documentation and issuing of blood components must be carried out with proper attention. Failing to do so can result in harmful adverse events. For instance, human errors that occur at the blood bank could lead to a fatal ABO incompatibility transfusion in the recipient. Undoubtedly, adherence to mindfulness can prevent sample mixing, erroneous interpretation and transcription errors made by the individual. With mindfulness person working at a blood bank can prioritize the urgent procedures while engaging in routine work. Moreover, activities that distract the person, such as using social media, could be discouraged with mindfulness.

Conclusion: In conclusion, mindfulness is a crucial aspect in maintaining the quality of the services provided by the transfusion service. Hence, blood bank training programs must include easily feasible mindfulness exercises to motivate the blood bank staff.

A044

Autologous serum eye drop manufacture and usage in Australia

Dr Joanne Tan[1,2], *Ms Roberta Dumbrava[4], Dr Peter Bentley[3], Dr Peta Dennington[1]*
[1]Australian Red Cross Lifeblood, Alexandria, Australia, [2]The University of Sydney, Camperdown, Australia, [3]Australian Red Cross Lifeblood, Perth, Australia, [4]University of Western Australia, Perth, Australia

Aim: The aim of this study was to clarify the indications and demand for autologous serum eye drop (AutoSED) products temporally and geographically within Australia. This audit was complemented by a survey of ophthalmologists to assist Lifeblood to anticipate future needs in the manufacturing and supply of AutoSED products.

Method: A retrospective audit of AutoSED products manufactured by Lifeblood supplied to patients between 2008 and 2018 was conducted. A survey was emailed confidentially to ophthalmologists (Qualitrics). Descriptive statistics on patient demographics, indications, accessibility and ophthalmic responses were analysed (IBM SPSS Program v23).

Results: A total of 2,485 AutoSEDs were manufactured in an 11-year period and distributed to 1,310 unique patients. Seventy-two percent of AutoSEDs were made for female patients (mean age 57 years) compared to 28% for male patients (mean age 53 years). There was an upward trend in AutoSED referrals from 145 products in 2008 to 355 products in 2018, with 60% of product manufactured in NSW. A significant proportion of patients receiving AutoSEDs had severe dry eye syndrome (39.3%), followed by immune-related conditions (13.1%) and non-immune non-dry eye conditions (9.5%). There were 26 responses to the survey with 69% of ophthalmologists stating that there was clinical utility and evidence to support AutoSED use. The use of allogeneic products (30%) and online referral systems by ophthalmologists (42%) were identified as potential enhancements to current Lifeblood referral and production practices.

Conclusion: Over the 11-year period studied, there has been increased demand for AutoSEDs. Females represented the majority of referrals, as did immune-mediated ocular indications. Ophthalmologists when surveyed indicated AutoSEDs to be objectively and clinically useful for their dry eye patients. As the vast majority of AutoSEDs were supplied for chronic eye conditions, the demand for AutoSEDs can be expected to continue to increase in future years.

A045

Blood donor health status influences red cell component quality during storage

Dr Joanne Tan[1,2], *Ms Yeojoon Cha[1], Ms Htet Htet Aung[1], Dr Ryan Hyland[1], A/Prof Catherine Hyland[3], Dr Helen Faddy[4], A/Prof Denese Marks[1,2]*
[1]Australian Red Cross Lifeblood, Alexandria, Australia, [2]The University of Sydney, Camperdown, Australia, [3]Australian Red Cross Lifeblood, Kelvin Grove, Australia, [4]University of Sunshine Coast, Moreton Bay, Australia

Aim: Whole blood donors are screened for haemoglobin levels and considered healthy when donating. Recent studies suggest an association between donor body mass index (BMI) and haemolysis in red cell (RBC) components from their donation. The aim of this study was to investigate associations between RBC component quality and donor attributes.

Methods: Whole blood donations collected from 792 consented donors were manufactured into RBC components. Haemolysis and extracellular potassium were measured on day 42 of storage. Serum ferritin concentration was measured from an additional pre-donation blood sample. Associations between RBC quality parameters and other donor attributes (sex and BMI) were investigated. Data were analysed by one-way ANOVA adjusted for multiple comparisons, and $p<0.05$ was considered significant.

Results: RBC components from donors with high ferritin (>200 µg/L; n=44) had significantly higher haemolysis at day 42 compared to RBC components from donors with low ferritin (<30 µg/L for males; <15 µg/L for females; n=140; p=0.0041), or RBC from donors with ferritin within the normal range (n=608; p=0.0006). RBC components from donors with high ferritin also had higher extracellular potassium than donors with low or normal ferritin (p=0.0011, p=0.0003 respectively). Donors with high ferritin also had higher BMI than donors with low or normal ferritin levels (p=0.0002, p=0.0136 respectively). RBC components from donors with high BMI (>25.0; n=428) had significantly higher haemolysis and extracellular potassium compared to RBC from donors with lower BMI (<25.0; n=364; both p<0.0001). In particular, male donors with higher BMI were had higher haemolysis and extracellular potassium than other male donors with low BMI and all female donors (both p<0.0001).

Conclusions: RBC components from donors with high ferritin levels had higher haemolysis and potassium release, as did RBC components from donors with high BMI. This suggests that blood donor health status could influence RBC component quality, warranting further investigation.

A046

A State Blood Inventory Manual - an important best practice tool

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Aim: Blood is a precious resource that is donated by volunteers and has the ability to both save and significantly improve the quality of life. From the donor to recipient, there are many critical and crucial steps to ensure blood and blood products are managed in a responsible, sustainable and appropriate way. Having a ready available tailored resource tool for local blood management was a necessity.

Method: *The Regional LHN Blood and Blood Products Inventory Manual* was first developed in 2014 and provides guidance to all country South Australia regional and remote health services on appropriate storage, transportation, inventory management which facilitates the minimisation of wastage of blood and blood products

Results: The Manual has sections outlining key areas of blood refrigeration that informs hospital staff of the requirements and the storage conditions for blood products. This section details important aspects such as temperature monitoring, alarm testing and servicing. Since blood products require transportation under regulated cold-chain conditions, a section on receipting blood, including correct unpacking of transportation shippers and subsequent packing when blood is rotated back to supplier. Importantly, there is a section that assists with the identification and resolution of quality failures with blood and blood products, refrigeration alarms and outages, and transportation shippers. A section also includes all forms, registers and “how to guides” related to blood and blood products, refrigeration and transport shippers. The Red Cell Return Form, Blood Refrigerator Maintenance Record, Blood Refrigerator Alarm and Outage Action Plan are some examples of these forms.

Conclusion: The Manual has shown to assist nursing and laboratory staff with their daily blood handling activities, the further enhance this tool a simplified, easy to read flip-book is being developed as a quick reference to assist clinical staff.

A047

Development of a mobile device based state blood inventory application

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Aim: Regional South Australia (SA) covers an area of approximately 1,000,000km^2. Regional SA has 35 hospitals that hold blood and blood products, 11 regional hospitals also have an SA Pathology laboratory on site. A state wide blood inventory application for mobile devices was developed with the aim to better facilitate blood management for all potential users.

Method: Using the current SA Blood and Blood Product Inventory Map and available site information a mobile device application was developed.

Results: Regional SA presents significant challenges to the supply and maintenance of emergency standby blood stocks due to distance from the Australian Red Cross Lifeblood Service in Adelaide. Stock rotation to high use metropolitan sites prior to expiry and cold chain assurance are additional challenges. BloodMove, a collaborative program between SA Health and public and private pathology laboratories aims to minimise blood wastage due to poor cold chain systems and product loss due to product expiry.

The inventory and emergency stock holdings of blood and blood products in regional hospitals is currently displayed on a hard copy map available at each SA public hospital, laboratory and also the SA medical retrieval service (MedSTAR). The SA Health Blood Inventory App has been developed to complement the current hard copy map. The App is inclusive of all metropolitan and regional laboratories and those regional sites holding emergency blood products. The standard inventory holdings include the total number of red cells expanded to all blood groups, fresh frozen plasma, platelets, cryoprecipitate and prothrombinex for each site.

Conclusion: The advantage of the App is that it is available for all medical retrieval services, all laboratory staff, management in SA Health and importantly readily available to inform contingency planning.

A048

Development of blood and blood product holdings for a state medical retrieval service and their use

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Aim: Blood support for MedSTAR, the South Australian medical retrieval service has evolved from daily rotation of three prepared shippers each with two units of emergency O Neg red cells (RC) since 2009 to a compliant monitored blood fridge being established at the MedSTAR base storing 8 units of O Neg RC being rotated fortnightly since 2015. New specialised blood shippers replaced the previous cumbersome shippers and allowed for increased capacity of red cell units taken on a mission. This extra availability of O Neg RCs enabled MedSTAR to replenish O Neg stock at a regional/ remote SA site when their O Neg RC stock was used for the patient being retrieved. In late 2018, a massive transfusion protocol (MTP) pack was introduced for blood product resuscitation of critical bleeding patients. This pack utilised a newly developed lightweight shipper with provision for RC, plasma and platelets. The aim of the study was to examine the blood and blood product use to manage patients during MedSTAR missions.

Method: Data on blood and blood product transfused including patient details collected during MedSTAR retrieval mission was analysed.

Results: The following table summarises the number of events that required red cell transfusion, total number of red cells transfused, red cells transfused per event including number of critical bleed events and associated MTP activations.

	Events	Red Cell Units (Total)	Red Cell Units (Mean)	Critical Bleed Events	MTP Activations
2018	86	148	1.7	19 (22.1%)	n/a
2019	108	193	1.8	42 (38.9%)	18
2020	77	124	1.6	38 (49.4%)	6

Conclusion: Red cells are commonly transfused during retrieval missions. The implementation of MTP pack has assisted with the resuscitation of patients with critical bleeds

A049

Tour of duty of O Negative red cells issued to South Australian transfusion laboratories

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Aim: An investigative exercise was undertaken to understand transfer history and fate of O Negative red cell units (RC) supplied by the Australian Red Cross Lifeblood Service to South Australian (SA) laboratories. Information was sought to investigate the high supply rate of O Negative RC in SA. This project is part of the BloodMove Program, a collaborative program to facilitate best practice in blood management through regional and metropolitan South Australia.

Method: BloodNet data on RC supplied to SA laboratories between 1 July 2020 and 30 December 2020 were linked to provide information on transfusion/discard fate and the transfers between laboratories. Transfusion fate could be confirmed for public sector sites using Laboratory Information Systems (LIS).

Results: Of the 4164 RC analysed, 2224 (53.4%), 1078 (25.9%) and 862 (20.7%) were supplied to metropolitan, regional and private providers respectively.

Of 645 O Neg RC, 590 (54.7%) of the O Neg supplied to regional sites were transferred to metropolitan sites including 55 RC from private sites. Overall, 88 (2.1%) O Neg RC were discarded. A total of 2844 and 461 RC were transfused at metro and regional sites respectively. The RC that were supplied to metropolitan or regional sites were transfused at a mean age of 24 days. The RC transferred from regional or private sites and transfused at metropolitan sites were transfused at a mean age of 37 days. A total of 1303 of O Neg RC were transfused to O RhD Negative patients, 1378 to O RhD Positive patients, 601 and 23 RC transfused to patients with other and unknown blood groups respectively.

Conclusion: Although there is minimal wastage of O Negative RC, initiatives such as staggered stock rotation plan and inventory adjustments may help to reduce high O Neg RC supply rates.

A050

New Zealand Blood Service: Performance validation of the Grifols MDmulticard®

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Background: The New Zealand Blood Service (NZBS) uses commercially available liquid antisera to phenotype patients and donors. Patients may require a full phenotype: -D, -C, -c, -E, -e, -K, -Fy^a, -Fy^b, -Jk^a, -Jk^b, -S, and -s if they have a higher risk of developing alloantibodies due to continuous transfusion support i.e. patients who have β-thalassemia or autoimmune haemolytic anaemia. A full phenotype using liquid antisera is costly and can take up to an hour to complete.

Aim: To reduce the cost and time associated with phenotyping using liquid antisera, NZBS assessed the Grifols MDmulticard® for phenotyping -Fy^a, -Fy^b, -Jk^a, -Jk^b, -S and –s by lateral flow technology. The test can be completed in 10 minutes and is more cost effective than liquid antisera. Our aim was to validate the performance of the Grifols MDmulticard® for routine phenotyping by NZBS Blood Banks and Reference Laboratory in New Zealand.

Method: All testing was performed by trained technical staff within NZBS National Red Cell Serology Reference Laboratory. Patient and donor samples which met specific criteria were phenotyped using the method outlined in the Grifols MDmulticard® package insert. The two parameters for evaluation were 1) Accuracy and 2) Precision.

Results: The Grifols MDmulticard® performed as expected and met the criteria for accuracy and precision. The product limitations state the possibility of interference from IgG coating, and this was seen in samples with a strong positive IgG DAT.

Conclusion: Reducing the time and cost of phenotyping were our primary objectives in validating the Grifols MDmulticard®; both of which were met. Additionally, the Grifols MDmulticard® proved to be easy to interpret and showed less variability than tube grading. NZBS validated the Grifols MDmulticard® for use on samples with a negative IgG DAT. Whether the Grifols MDmulticard® is suitable for use after EGA treatment is worth further investigation so that patients with a strong IgG DAT due to autoimmune haemolytic anaemia may be phenotyped using this technique in future.

Conflict of interest statement:
This research was supported by Grifols Australia PTY Ltd. The company had no role in analysing the data or preparing the abstract.

A051

Modelling the predictors of platelet transfusion

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Background: Platelets are a valuable medical resource that must be utilised efficiently to optimise economic and health outcomes. In rural hospitals, it is not feasible to store liquid platelets due to their seven-day shelf life leading to rapid expiry and high levels of wastage. Cryopreserved platelets have a shelf life of up to two years and could help to rectify the unmet need of rural patient populations. Determining which hospitals would be justified in storing cryopreserved platelets requires assessment of the predictors of platelet use.

Aim: To analyse patient characteristics from a large registry of adult patients who received any blood product transfusion at participating hospitals in 2017. To develop a model that predicts platelet transfusion.

Method: Data from a large transfusion registry was analysed, with machine learning employed to identify important patient demographic, clinical and laboratory variables to develop a model that predicted platelet transfusion. The model was applied to data from a regional hospital without routine access to liquid platelets to quantify the number of patients who would have received platelets had they been available.

Results: The transfusion data from two metropolitan hospitals for the period of 1 Jan 2017 to 31 Dec 2017 were analysed. A total of 8,184 patients were transfused with any blood product. There were 10,813 platelet transfusions. The variables that predicted platelet transfusion were extracted and evaluated to form a model that predicted platelet transfusion based on patient characteristics.

Conclusion: The model developed in this project demonstrates variables that determine platelet transfusion. Into the future, it could assist in determining which hospitals should store cryopreserved platelets should they become available for mainstream medical use. Ultimately, it could lead to better access to platelets and may improve clinical outcomes for patients.

A052

Implementing an electronic medical record (EMR) at Monash Health: early experience from the transfusion clinical and laboratory perspective

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Title: Implementing an electronic medical record (EMR) at Monash Health: early experience from the transfusion clinical and laboratory perspective

Aim: To share initial experience of the transfusion-related aspects of implementing Cerner Powerchart at Monash Health - a large metropolitan health service.

Methods and Results: A multidisciplinary planning and implementation team worked together before and after “go live” in August 2019, with representation from transfusion laboratory scientists, transfusion nurses, lab IT, and medical staff. The process was overseen by our blood management committee and supported by the EMR provider with training modules and materials, on-site EMR staff, and trained hospital ‘super-users’. Roll-out was staggered across the network.

Examples of transfusion-related challenges, and how they were addressed, include:

- Developing an EMR-compatible process for pre-transfusion samples, which have specific labelling requirements, but are often ordered and collected at the same time as other tests.
- Blood bank interface: the Cerner system was required to interface with MediPath LIMS and to ensure EMR orders (including special requirements) were transferred across system interfaces.
- EMR order-set optimisation: with many different blood products available, the order-set needed to contain all essential information, while still being usable.
- Blood administration: multiple changes were required to allow for easier viewing of administered products, to be compliant with ANZSBT requirements, and to manage real-time information on product availability. Additional changes were required to manage certain multi-dose products (e.g. cryoprecipitate usually dosed at 5-10 units but supplied in individual units), where the system required additional work when documenting administration.
- Massive Transfusion Protocol: Paper-based prescribing and ordering was used, especially during the initial roll-out.
- Inpatient vs outpatient transfusion: The system did not accommodate attaching a transfusion order to an encounter in advance, requiring paper-based ordering and administration.

Conclusion: Designing and implementing an EMR requires understanding the complexity of transfusion support and special consideration and management of the clinical/laboratory interface. Our multi-disciplinary approach enabled prompt identification of issues and collaborative problem-solving

A054

A retrospective review of TRALI cases reported to the Australian Red Cross Lifeblood

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Aim: Transfusion-associated acute lung injury (TRALI) is a rare but serious adverse transfusion reaction. Suspected cases should be reported to Australian Red Cross Lifeblood for further investigations due to donor management implications. We conducted a retrospective review of TRALI cases reported to Lifeblood to describe the epidemiological and laboratory features of TRALI.

Method: Lifeblood's Adverse Transfusion Reaction database was accessed to identify all cases of suspected TRALI reported to Lifeblood from July 1st 2015 to June 30th 2019. For confirmed cases of TRALI the following information was collected: patient demographics, antibody investigation results, type of product implicated, age of products, donor gender and donor outcomes. Statistical analysis was performed using Fisher's exact test.

Results: Of the 59 cases of suspected TRALI, expert review confirmed 23 as TRALI. An additional TRALI case was initially reported as an allergic reaction. Of the 24 confirmed TRALI reactions, 15 were classified as TRALI and 9 as possible TRALI. A total of 62 components from 81 donors were implicated. Forty-nine (60%) of these donors were male, 31 (38%) female and 1 (1%) unknown (cadaveric liver). Thirty-three (41%) of these donors were deferred, of which 18 (55%) were men, and 15 (45%) were women. Sixteen cases (67%) were associated with donor antibodies, most commonly anti-HLA class I and anti-HLA class II antibodies that were non-recipient specific. Anti-HNA antibodies were present in 3 cases. There were 8 cases in which an antibody was not implicated. There was no difference in antibody detection rates between low plasma volume components (red cells, pooled platelets and cryoprecipitate) and high plasma volume components (fresh frozen plasma and apheresis platelets) (45% versus 34%, p=0.44).

Conclusion: TRALI is a rare condition and further studies are required to improve our understanding of its pathophysiology and laboratory findings.

T002

Perioperative management of patients with hemophilia (PwH) receiving fitusiran prophylaxis with reduced doses of BPA or factor replacement

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Aim: Fitusiran is an investigational, once-monthly, subcutaneously administered siRNA therapeutic that targets antithrombin (AT) to restore sufficient thrombin generation (TG) and rebalance effective hemostasis in people with hemophilia A (HA) or B (HB), with or without inhibitors. Here we describe the hemostatic coverage for major surgical procedures, with reduced doses of factor or BPA, in PwH on fitusiran prophylaxis in the Phase 2 open-label extension (OLE) study (NCT02554773), based on *in-vitro* TG studies, modelling data and clinical experience.

Method: The Phase 2 OLE study included males who were ≥18 years of age, with moderate or severe HA or HB, with or without inhibitors. Participants received fixed monthly subcutaneous doses of fitusiran, 50 or 80 mg. Data were collected for participants who had major surgical procedures while on fitusiran.

Results: Seven of 34 participants in the OLE study, aged 27–57 years, underwent a total of 8 major surgeries (premolar tooth extraction, nasal septoplasty, molar tooth extraction, thoracotomy and partial lung segmentectomy, endoscopic cholecycectomy, total left knee joint replacement, metal plate removal and total right hip replacement, bilateral total knee replacement) while on fitusiran. The AT level before the procedures was <20% relative to baseline. Perioperative hemostatic treatments (FVIII, rFVIIa, and/or aPCC) were administered for 7 of the 8 procedures, with 5 participants receiving reduced doses and 2, standard doses of factor or BPA. Thromboprophylaxis was not used in any of the procedures. No thrombotic events were reported. The blood loss for all procedures was rated by the respective investigator as minimal or similar to an individual without hemophilia.

Conclusion: These results support the successful perioperative management of participants receiving fitusiran prophylaxis to date with reduced dosing of factor or BPA in limited but major surgeries in the Phase 2 OLE study. Additional data are needed to further define appropriate perioperative hemostatic management plans.

T003

Rapid Laboratory Diagnosis of VITT - A case report

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Rapid Laboratory Diagnosis of VITT – A case report

Vaccine induced thrombocytopaenia with thrombosis (VITT) is a rare complication seen post administration of the ChAdOX1 nCoV-19 adenoviral vector vaccine. The phenomenon is characterised by simultaneous venous thrombosis and thrombocytopaenia which presents within a short time (typically 4-28 days) after vaccination[1]. Early case studies have reported similarities in molecular mechanisms and clinical characteristics between VITT and heparin induced thrombocytopaenia with thrombosis (HITT)[2,3]. These similarities are such that some of the current laboratory techniques used to screen for HITT are also being utilised to detect the antibodies that appear to be responsible for VITT. While the clinical utility of these techniques in VITT are still being determined, a major limiting factor in their use is a lack of widespread availability and relatively long turnaround times which can delay critical clinical decisions in an acute setting. Here we describe a case report of a patient with VITT and the potential use of a rapid diagnostic functional platelet activation assay performed on the Multiplate®, which can assist in the early detection of VITT related antibodies.

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T004

Laboratory measurement of emicizumab levels by one stage and chromogenic assays

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Aim: Emicizumab is a recombinant, humanised bispecific antibody which binds to and bridges FIXa and FX, thus acting as a FVIII mimetic. Assay of plasma emicizumab levels in treated individuals may sometimes be needed to assist patient management. Our objective was to determine the performance characteristics of six one-stage clotting assays (OSA) and a chromogenic assay (CSA) in measurement of plasma emicizumab.

Method: The APTT reagent/analyser combinations evaluated were: Actin FS and Actin FSL on the Sysmex CS2500; Triniclot aPTT S and PTT A on the STA-R; Synthasil and APTT SP on the ACLTOP750. The Hyphen chromogenic FVIII kit was used on the CS2500. Commercial emicizumab calibrators and controls, emicizumab spiked into FVIII deficient plasma, and five patient samples were used to assess accuracy, precision and spike recovery.

Results: Replicate precision of high or low control material CVs varied from 1.3% to 4.4% across APTT reagents, with between run CVs varying from 3.0% to 7.4%, For very low levels replicate and between run precision CVs varied from 0.8% to 8.7% and 3.5% to 12.6%, respectively. Mean emicizumab recoveries of spiked samples were within 20% of target for all six spike levels, and 81% of all recoveries were within 10% of target. Assay variability of ex-vivo samples of patients treated with emicizumab were largely equivalent to spiked sample assay variability. There was good freeze-thaw stability of reagents

Conclusion: Emicizumab assays can be readily automated on different coagulation analysers, using commonly used APTT reagents and FVIII deficient plasma, as well as the Hyphen CSA. The assays showed good precision, accuracy and linearity.

T005

Utility of the "Young Stroke" workup – a retrospective analysis on thrombophilia testing in patients with ischaemic stroke

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Aim: Ischaemic stroke is a major health problem and almost 25% occur in patients under 65 years of age. These cases are often extensively investigated, although the utility of universal thrombophilia testing is unknown. We conducted a retrospective audit examining thrombophilia testing in patients with ischaemic stroke admitted to our institution.

Method: We reviewed the clinical and laboratory data on a selection of those with ischaemic stroke admitted to RPA Hospital, Sydney, between Jan 2018 and Dec 2020 who had a thrombophilia screen performed. We collected demographic data, characteristics of stroke, and results of thrombophilia testing.

Results: A total of 127 patients were included with a median age of 52 years (range 20-80). 67% of patients were male. The most common tests ordered were Factor V Leiden mutation (FVL, 95%), prothrombin gene mutation (PGM, 91%), antithrombin level (AT, 99%) and lupus anticoagulant (LAC, 97%). Of these, 3 had PGM, 3 FVL heterozygous and 11 had at least one positive test for antiphospholipid syndrome. Factor VIII level (FVIII) and von Willebrand factor (vWF) were performed in some cases, which revealed abnormal results (high levels) in 27% and 19% respectively. We found only 2 of the 127 patients had a change in management due to the results of this testing.
Tests performed and positive rates are shown in the table below.

			Age, years (no. [%])		Sex (no. [%])	
Test	**Total Tests**	**Total Abnormal Tests (no. [%])**	**20-51 (n=63)**	**52-80 (n=64)**	**Male (n=85)**	**Female (n=42)**
FVL	121	3 (2.47%)	1	2	2	1
PGM	116	3 (2.58%)	1	3	3	0
AT	126	2 (1.58%)	2	0	1	1
LAC	123	3 (2.44%)	2	1	1	2
Anti-cardiolipin	86	8 (9.3%)	4	4	3	5
Beta-2-glycoprotein	41	0	0	0	0	0

Conclusion: Thrombophilia testing is frequently performed in the setting of ischaemic stroke, with low rates of positive results, and even fewer leading to a change in management. Appropriate guidelines in the use of thrombophilia testing in this setting should be established to allow for more targeted testing.

T006

A case of treatment-responsive acquired von Willebrand's disease as a manifestation of newly diagnosed multiple myeloma

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Introduction: Acquired von Willebrand's disease (AVWD) is a rare but well-described paraneoplastic phenomenon in paraproteinaemias, with bleeding phenotypes often failing to demonstrate sustained response to treatment of the causative disorder and IVIG and/or exogenous factor replacement required on an as-needed basis to prevent or arrest clinically significant bleeding. We present a case of acquired AVWD as a presenting complaint of multiple myeloma, demonstrating response to myeloma-specific treatment both in terms of laboratory tests of haemostasis and bleeding phenotype.

The Case: A 73 year old male patient was referred to our hospital's haemophilia and thrombosis clinic for a history of excessive intra-operative bleeding, with no prior personal or family history of bleeding diathesis. Further testing demonstrated a prolonged APTT that corrected on 50:50 mixing, and marked reduction in FVIII-c, vWF antigen, ristocetin assay and collagen binding assay indices. Bethesda assay screening for inhibitors of both FVIII and vWF were negative. The patient was found to have a 10 g/L IgG kappa paraprotein. Treatment with IVIG produced temporary correction of vWF indices permitting bone marrow aspirate and trephine, which found a 20% plasmacytosis. Treatment with lenalidomide and dexamethasone produced sustained reduction in paraprotein to 2 g/L, accompanied by normalised vWF indices and no further minimally traumatic bleeding.

Discussion: In the rare instance of AVWD secondary to paraproteinaemia, treatment of the underlying cause often fails to produce correction in bleeding phenotype if there is persistence of the causative paraprotein. Our case demonstrates the possibility that myeloma-specific treatment can produce improvement in both clinical bleeding phenotype and commonly available laboratory assessments of haemostasis even where elimination of the paraprotein is not achieved. This may produce the added benefit of obviating need for exogenous factor replacement.

T007

The Factor VIII genetic mutation profile of a cohort of New Zealand patients with Haemophilia A

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Background: Knowledge of the specific Factor VIII (FVIII) mutation present in individuals with Haemophilia A (HA) is important for carrier identification and risk estimation of inhibitor formation. We sought to investigate the mutational profile of patients who had undergone *F8* molecular testing at our centre.

Method: A retrospective cohort study was conducted of all HA patients who had undergone *F8* mutation analysis between 01/01/2000 and 30/04/2021 and their known kindreds. This involved long range allele-specific PCR for intron 1 and 22 inversions in severe disease (FVIII:C <1%) and Sanger sequencing in others. Patient demographics, clot-based FVIII activity and inhibitor status were obtained from the clinical record.

Results: Mutation analysis was available on 148 individuals from 128 unrelated families with HA, (71% of all patients in our regional database). Median age was 34.5 years and 15% were Māori (35% of those with severe disease). A *F8* mutation was identified in 99.3% patients, with 65 different mutations across 128 families. Nine novel mutations were seen. Missense mutations accounted for nearly all mild and moderate disease (93% and 88%, respectively). Severe patients had predominately intron 22 inversions (58%). No statistically significant association was seen between ethnicity and mutation type. Inhibitors were identified in 19 patients (2 mild, 1 moderate, 16 severe). Māori and Pacific patients were significantly over-represented ($p < 0.01$). A statistically significant association between inhibitor presence and intron 22 inversions or large deletions was not seen.

Conclusion: This is the largest cohort analysis of *F8* mutations from NZ. Intron 22 inversions and large deletions in severe disease were more common than other populations, which was not explained by ethnicity alone. Māori and Pacific patients were significantly over-represented in those with inhibitors. The lack of association with intron 22 inversions or large deletions suggests the mutational profile contributing to inhibitor development may be more heterogenous than reported elsewhere.

T008

96-well Optimul assay in a regional Australian context

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Aim: Light transmission aggregometry (LTA) is considered the "gold standard" diagnostic test of platelet function. This requires expertise to perform and interpret aggregation traces and is almost universally unavailable in regional centres across Australia. 96- well plate based aggregometry, OPTIMUL, was developed by collaborators in the UK to provide simple and robust platelet functional analysis, applicable to regional sites and smaller metropolitan hospitals. We evaluate the use of OPTIMUL in Australia with the aim of assessing its feasibility as a screening test in regional centres.

Method: Platelet function was assessed in 65 healthy individuals using the OPTIMUL assay at Prince of Wales Hospital (POWH) through the Sydney Platelet Group, and Lismore Base Hospital (LBH). For comparison, testing for patients at POWH was run parallel to standard LTA. Agonist dose response curves were generated using excel data templates and PRISM graphpad. Samples from additional groups were tested as listed below:

Table 1: Populations tested by **OPTIMUL**

Patient Group	No. of patients (Lismore Base Hospital)	No. of patients (POWH)
Patients with known platelet disorders	1 (*RUNX-RT*)	0
Patients with unknown platelet disorders	11	8
Patients on aspirin	2	2
Patients on clopidogrel	2	0
Patients on combined aspirin and clopidogrel	1	0
Patients on NSAIDS	2	0

Results: A dose-response relationship was demonstrated with all 7 agonists using OPTIMUL in patients at both centres. By combining the dose-response curves for each patient, separate 'control curves' were successfully generated at both testing sites. OPTIMUL detected anti-platelet effects of Aspirin, clopidogrel, as well as, non-steroidal anti-inflammatories. 12 healthy patients had platelet function testing performed using both OPTIMUL and LTA with 92% concordance between the two tests.

Conclusion: The OPTIMUL assay is an easy to use method providing detailed platelet function testing with potential applicability in both a regional and metropolitan laboratories.

T011

Rationale for and design of the XTEND-1 Phase 3 study to evaluate efanesoctocog alfa, a new class of factor VIII (FVIII) replacement, in severe hemophilia A

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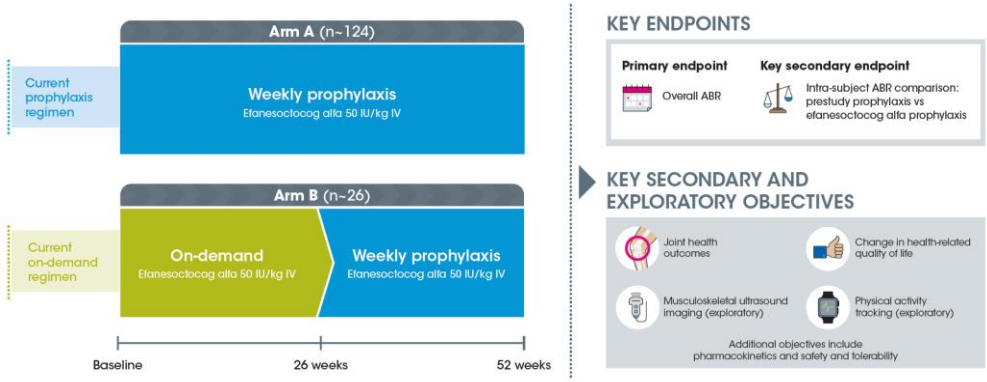
Method: Hemophilic arthropathy remains a major cause of morbidity for people with hemophilia. Despite regular prophylaxis, bleeding events continue to occur, sometimes subclinically, leading to progressive joint damage. Target FVIII levels are being reevaluated as scientific evidence increasingly suggests that previously accepted levels are insufficient to maintain joint health. Efanesoctocog alfa (BIVV001) is a novel fusion protein designed to decouple FVIII from endogenous von Willebrand factor (VWF), leading to high sustained FVIII activity. In a Phase 1 repeat-dose study, once-weekly efanesoctocog alfa (50 IU/kg) (40 hour half-life) resulted in mean FVIII activity levels in the normal to near-normal range (>40%) for 3 days post-dose and 10% (5–16) on Day 7. Efficacy, safety, and pharmacokinetics of efanesoctocog alfa are being evaluated in 3 multicenter, open-label, non-randomized Phase 3 clinical trials (XTEND-1, ≥12 years, NCT04161495; XTEND-Kids, <12 years, NCT04759131; extension, XTEND-ed, NCT04644575).
This study describes the XTEND-1 study design, including novel endpoints to assess joint health and physical activity.
For XTEND-1, previously treated patients with severe hemophilia A (<1% endogenous FVIII) are eligible for inclusion. Subjects on pre-study prophylaxis receive prophylaxis with once-weekly efanesoctocog alfa 50 IU/kg for 52 weeks (Arm A). Those on pre-study, on-demand treatment receive efanesoctocog alfa 50 IU/kg on demand for 26 weeks before switching to the prophylaxis regimen for 26 weeks (Arm B) (Figure).

Results: The primary efficacy objective is to evaluate efanesoctocog alfa prophylaxis, as measured by overall annualized bleeding rate (ABR). The key secondary endpoint is intra-patient ABR comparison in Arm A (pre-study vs efanesoctocog alfa prophylaxis). Joint health endpoints include joint ABR, target joint resolution, and changes in hemophilia joint health score. Additional endpoints include patient-reported outcomes related to pain, quality of life, changes in structural joint health outcomes via ultrasound imaging, and changes in physical activity using wearable devices.

Conclusion: XTEND-1 is currentlyongoing.



ABR, annualized bleed rate; IV, intravenous.
Joint health outcomes include Hemophilia Joint Health Score (HJHS), target joint resolution, and joint ultrasound using the Joint Tissue Activity and Damage Examination (JADE) protocol in Musculoskeletal Ultrasound (MSKUS) and/or Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US).

T012

Mapping platelet response to thrombin using high-sensitivity platelet proteomic analysis

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Aim: Platelets respond to agonists (e.g. thrombin) by the secretion of intracellular proteins and mediators which promote thrombus formation [1]. There are limited studies regarding global protein changes after thrombin stimulation in healthy individuals [2]. Our study aims to establish high-quality characterisation of the healthy platelet proteome, at baseline and after thrombin stimulation.

Method: Platelets were isolated from whole blood from healthy volunteers. Baseline PAC-1 and CD62P expressions were determined by flow cytometry. Platelets were stimulated with submaximal (0.025U/mL, n=5) and high dose (0.20U/mL, n=6) thrombin. Proteins from the platelet releasate and lysate were identified and quantified using the Thermo Lumos Tribrid Orbitrap mass spectrometer. Protein secretion was determined using a novel method of protein abundance anti-correlation between the lysate and releasate. Statistical analysis was by R and plotted using Tableau. Significance was determined using a repeated-measures one-way ANOVA for activation (resting vs thrombin) at P<0.05.

Results: Platelet activation markers PAC-1 and P-selectin were expressed on <0.5% and <15 % of isolated platelets respectively. Plasma contamination of the platelet preparation was <0.5%. Qualitative changes were seen in platelet proteins secreted after high (**Figure 1**) and submaximal dose thrombin, with 203 and 74 proteins that were significantly increased respectively. There was a significant increase in proteins associated with platelet aggregation (e.g. thrombospondin-1) as expected, but also proteins associated with inflammation (e.g. CXCL3), angiogenesis (e.g. VEGF-C) and yet undetermined platelet functions (e.g. alpha-(1,6)-fucosyltransferase) [3].

Conclusion: Our platelet proteomic platform provides a resource to study proteins mobilized by platelets for a spectrum of functions, beyond haemostasis. Further investigations regarding proteomic differences and post-translational modifications may yield novel protein markers and therapeutic targets in disease states.

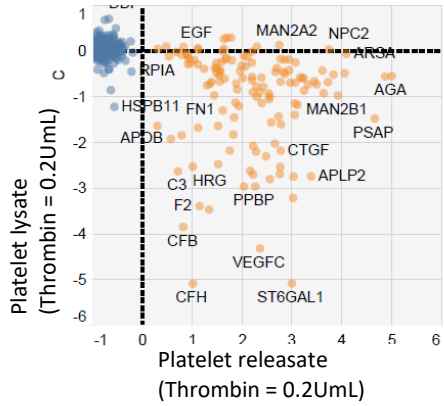

Figure 1 (right): Platelet releasate and lysate proteomes after stimulation with thrombin 0.2 U/ml. Dots represent individual proteins. Proteins in orange are significantly increased in the releasate and decreased in the lysate following stimulation.

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T013

Coagulopathy: an underrecognised complication of acquired HLH

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Aim: Acquired haemophagocytic lymphohistiocytosis (aHLH) is a rare and often fatal process of uncontrolled cytokine release and macrophage activation. Thrombocytopenia and hypofibrinogenemia are recognised features, though the mechanisms are not fully understood, and bleeding complications are poorly described. Herein we describe two cases of unexpected major haemorrhage despite in patients with aHLH despite appropriate correction of numerical coagulation abnormalities.

Method: Retrospective case series. Data collected included the diagnosis, treatment, complications and outcomes.

Results: Two cases of acquired HLH were confirmed using HLH-2004 criteria and H-score. The first case was a seventy-five-year-old male who developed unrelenting aHLH following *Pseudomonas aeruginosa* bacteraemia. Persistent FGD-PET-avid pulmonary infiltrates required percutaneous biopsy to exclude lymphoma. Despite correction of coagulopathy and platelet count with transfusion (PT 10, APTT 37, Fib-C 1.9, platelets 66), the patient suffered a major and ultimately fatal pulmonary haemorrhage.

The second patient was a thirty-one-year-old male who presented with aHLH due to systemic Epstein-Barr virus infection. He had rapidly progressive acute hepatitis, leading to laparoscopic liver biopsy before the diagnosis of aHLH was secure. Despite appropriate correction of underlying coagulopathy and thrombocytopenia with blood product support (PT 11. APTT 50, Fib-C 1.9, platelets 99), major haemorrhage occurred over the ensuing week requiring multiple blood transfusions, product replacement and laparotomy for abdominal compartment syndrome. Haemorrhage did not cease until the addition of tranexamic acid and control of the HLH with the HLH-94 protocol.

Conclusion: Severe coagulopathy is associated with increased mortality in aHLH. However, this may reflect the underlying severity of the aHLH itself rather than haemorrhagic complications. As patients with HLH often need biopsies to establish a diagnosis, bleeding may be an underrecognised complication requiring a careful consideration of risks versus benefits. As thrombocytopenia and hypofibrinogenaemia appear to play a significant pathogenic role, aggressive platelet transfusion, cryoprecipitate and tranexamic acid are critical.

T014

Caplacizumab induced rapid recovery of platelets in a multiply relapsed Thrombotic Thrombocytopenic Purpura

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Aim: Thrombotic Thrombocytopenic Purpura (TTP) is a life-threatening medical emergency and has the hallmark features of microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia. We report a case with multiple relapsed refractory TTP over four decades, treated with compassionate access Caplacizumab that led to rapid platelet recovery and reduced requirement for daily total plasma exchange (TPE) during the COVID19 pandemic.

Method: We report a 73 year old man with relapsed refractory TTP since 1983 with relapses every 2 to 5 years sometimes complicated by thrombosis as well as stroke, persisting ADAMTS13 activity <1% and positive inhibitors during relapses. He has received many different treatments including prolonged plasmapheresis usually over weeks and sometimes twice a day, steroids, splenectomy and Rituximab on a background of Type 2 diabetes. He had spontaneous TTP relapse in August 2020, during the COVID19 pandemic, where routine bloods showed moderate thrombocytopenia and moderate schistocytes on blood film. Urgent daily plasma exchange was commenced with Prednisone 1mg/kg daily. Caplacizumab was commenced with an intravenous dose prior to the second plasma exchange, followed by ongoing subcutaneous daily therapy for 45 days.

Results: Platelet count rapidly normalised within 3 days, and daily plasma exchange occurred for 4 procedures only, followed by a 5th and final procedure 4 days later. Due to a recurrence of a detectable ADAMTS-13 inhibitor of 2.5 Bethesda units, Rituximab weekly for 4 weeks was given. There were no treatment concerns, no thrombotic complications, and the patient remains in a solid durable remission.

Conclusion: Caplacizumab, a novel nanobody that prevents the interaction between von Willebrand multimers and platelets to reduce aggregation resulted in rapid platelet recovery, prevention of thrombotic complications and reduced in hospital management during the COVID19 pandemic.

T015

Analysis of thrombophilia testing practices at a regional teaching hospital

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Aim: Routine testing for thrombophilia is not recommended by clinical guidelines. Testing rarely changes the acute management of a thrombotic event. Despite this, there is a wide variation in practice with testing often performed for inappropriate clinical indications with incomplete testing and follow up. This may lead to mismanagement of low-risk thrombophilia and inaccurate interpretation of negative results without considering other patient-specific risk factors. Indiscriminate testing also poses a financial burden on the health system.

This retrospective audit reviewed thrombophilia testing performed at Sunshine Coast University Hospital over a six-month period to evaluate clinical indication and utility in guiding management. The intent was to identify potential areas for improvement.

Method: Data was collated from electronic medical records for all adult patients who received thrombophilia testing between 1 June to 31 December 2019. This included heritable thrombophilias, antiphospholipid antibodies, PNH flow and/or JAK2. Clinical information was gathered regarding indication, accuracy, and outcomes.

Results: Overall, 119 patients received 955 thrombophilia tests. 52 (44%) panels were performed for investigation of stroke, 24 (20%) for venous thromboembolism, 17 (14%) for non-stroke arterial thrombosis and 8 (7%) for pregnancy related conditions. In the subset of patients with venous thromboembolism, 15/24 (63%) had provoking factors and were tested inappropriately. In 30/46 (65%) patients with ischaemic stroke, alternative causes were later identified after completion of diagnostic evaluation. A positive result occurred in 36 (30%) cases overall, leading to a change in patient management in 4 (3%). 53 (44%) of thrombophilia screens were associated with situations of reduced accuracy including acute thrombosis, anticoagulant use, and pregnancy.

Conclusion: Inappropriate thrombophilia testing continues despite evidence of limited utility and accessibility of guidelines recommending against indiscriminate use. Ongoing clinician education remains key to improving testing practices, in conjunction with consultation with haematology services.

T016

Refractory Immune Thrombocytopaenia Treated with Tocilizumab: A Case Report

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Introduction: Refractory immune thrombocytopenia (ITP) can be a challenging condition to manage. It is associated with significant risk of bleeding and potential decreased quality of life. Refractory patients can quickly progress through treatments being placed at risk of the complications of immunosuppression.

Patient Presentation: We report a 25-year-old patient with a longstanding history of familial ITP, who presented with thrombocytopenia and widespread petechiae who was refractory to several treatments including corticosteroids, intravenous immunoglobulin, rituximab, splenectomy, eltrombopag (which precipitated widespread arterial and venous thrombosis) and cyclosporine. Despite extensive investigations, including multiple bone marrow aspirate and trephine samples, flow cytometry, red cell scanning, various infectious serologies and a specific genetic panel, no secondary cause was identified. His life was restricted from multiple complications and presentations to hospital.

Clinical Course: A recent diagnosis of HHV8-negative Castleman's disease from an isolated left lymph node, consistent with a monotypic and monoclonal plasmacytosis, (initially PET avid) led to the trial of tocilizumab, a monoclonal antibody to interleukin (IL)-6, for management of his ITP. It was theorised that a pro-inflammatory environment was driving his long-standing ITP. Shortly, after commencement of tocilizumab a complete response was achieved within two weeks. After four monthly infusions, no further doses were required. Response was sustained to a year post-treatment.

Discussion: To our knowledge, this is the first report of ITP successfully treated with tocilizumab. It may highlight the importance of pro-inflammatory cytokines in the pathophysiology behind refractory ITP, resistant to B-cell therapies.

T017

Global coagulation assays and endothelial biomarkers in patients with diabetes mellitus

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[1]Northern Health, Epping, Australia, [2]Australian Centre for Blood Diseases, Melbourne, Australia, [3]University of Melbourne, Parkville, Australia

Aim: Diabetes mellitus (DM) is associated with increased risk of cardiovascular disease. There are no current coagulation studies that predict thrombotic risks. We aim to investigate the utility of global coagulation assays and endothelial biomarkers in diabetic patients compared to normal controls.

Method: Diabetic patients, not on anticoagulation and without active malignancy, were recruited from endocrinology outpatients. Blood samples were collected for baseline tests and global coagulation assays including thromboelastography (TEG), calibrated automated thrombogram (CAT) and overall haemostatic potential (OHP) assay as well as tissue factor pathway inhibitor (TFPI) and plasminogen activator inhibitor-1 (PA1-1). The results were compared to previously recruited healthy controls (n=153).

Results: 184 patients consisting of 22 type 1 DM (T1DM), 154 type 2 DM (T2DM) and 8 latent autoimmune diabetes in adults (LADA) were recruited. Compared to normal controls, diabetic patients demonstrated more hypercoagulable TEG parameters with increased clot strength (maximum amplitude, 68.7 vs 60.5 mm, $p<0.001$). While there was no difference in thrombin generation (CAT), the OHP assay demonstrated significantly higher fibrin generation and lower overall fibrinolytic potential (OFP 73.6 vs 81.1%, $p<0.001$). TFPI was significantly increased in diabetic patients (36.9 vs 14.5 ng/mL, $p<0.001$) while PAI-1 was comparable ($p=0.14$). On sub-analysis, T2DM patients were more hypercoagulable than T1DM patients on thromboelastography, and fibrin generation with higher PAI-1 (14.8 vs 8.7 ng/mL, $p=0.017$) but comparable for other assays. T1DM patients with known diabetic complications had lower OFP than those without complications while T2DM with known complications had higher thrombin generation parameters with reduced OFP.

Conclusion: Our study demonstrates that diabetic patients have a more hypercoagulable profile on global coagulation assays, particularly in T2DM patients as well as patients with known diabetic complications. Further studies with longer term follow-up are ongoing to evaluate the utility of global coagulation assays in predicting patient outcomes.

Relapse of immune thrombocytopenic purpura (ITP) following ChAdOx1 nCoV-19 (AstraZeneca) vaccine

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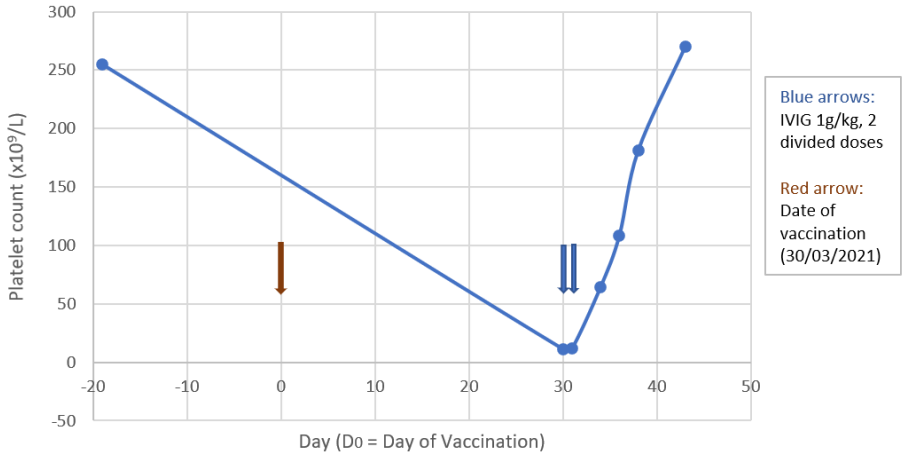
Background: The current worldwide COVID-19 vaccination effort is highlighting the risk of development or relapse of ITP with vaccination. Twenty cases of symptomatic thrombocytopenia post vaccination with either the BNT162b2 mRNA (Pfizer) or the mRNA-1273 (Moderna) SARS-CoV-2 vaccines are reported (1). A purpuric rash with thrombocytopenia has also been reported following the Moderna vaccine (2) and a case of severe refractory thrombocytopenia (3). We submit a case report of relapsed ITP following COVID-19 vaccination with ChAdOx1 nCoV-19 (AstraZeneca). Patient consent was received for publication of this report.

Case Report: MF is a 73 year old female with a history of refractory ITP in remission since her last treatment in 2011. She was sent to The Canberra Hospital by her GP 30 days after her first AstraZeneca vaccine. She complained of headache and was found to have a platelet count of $6x10^9$/L. A cerebral venous sinus thrombosis was excluded on computed tomography venogram. Repeat bloodwork confirmed thrombocytopenia of $11x10^9$/L and no evidence of platelet clumps or abnormal morphology. Coagulation studies showed a normal fibrinogen of 2.3 g/L, and her D-dimer was mildly elevated at 0.79 mg/L (ULN 0.50 mg/L).

She received intravenous pooled immunoglobulin 2g/kg, in two divisions, and had a marked increment in her platelets to $64x10^9$/L within 3 days of presentation, and up to $108x10^9$/L on day 5. By day 9, her platelets were $270x10^9$/L. Repeat D-dimers 5 days after presentation were only 0.81 mg/L.



Conclusion: Despite her marked thrombocytopenia, the absence of severely raised D-dimers was reassuring that pathogenic platelet activation and thrombin generation was unlikely. This case shines light on a less-described phenomenon of ITP relapse following immunisation. To our knowledge there appears to be no published cases of relapsed, established ITP following AstraZeneca vaccination.

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T019

A curious case of heparin resistance

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Introduction: Unfractionated heparin (UFH) is a sulphated glycosaminoglycan used intravenously as an immediate acting anticoagulant in acute thrombosis. The anticoagulant effect of UFH is routinely monitored using the activated partial thromboplastin time (APTT). Heparin resistance is defined as the requirement of high doses of UFH (>35000 IU/day) to achieve therapeutic APTT values. In the acutely ill patient, numerous plasma substances may interfere with both the action of heparin and the accurate measurement of the APTT, causing both true and apparent heparin resistance.

Method: Case study, laboratory investigations and literature review.
We present the case of a 65-year-old man who was admitted to the emergency department with abdominal pain. He was diagnosed with acute pancreatitis complicated by splanchnic vein thrombosis. He had a long-standing history of chronic renal impairment which contraindicated direct oral anticoagulant (DOAC) use, and UFH therapy was initiated. However, despite increasing doses of UFH over several days his APTT remained subtherapeutic.

Results: Our investigations highlighted some of the issues in heparin monitoring. In particular, our testing showed extremely high factor VIIIc levels in this patient, ranging from 2.61 to 5.51 IU/mL. Factor VIII is often elevated in the acute phase reaction, thus complicating heparin monitoring in acutely ill patients. Our testing also demonstrated the effect of a possible variant antithrombin on heparin monitoring.

Conclusion: Safe and effective management of UFH anticoagulation is most often dependent on the APTT being a reliable measure of anticoagulation. Heparin resistance, both true and apparent, can complicate monitoring of heparin, particularly in acutely ill patients. While the use of DOACs are increasing, the use of UFH is unavoidable in a subset of patients where these agents are contraindicated. Therefore, the limitations of the APTT in monitoring UFH tool must be well understood by the laboratory to ensure optimum care for patients.

T020

A real-world experience of venous thromboembolism (VTE) management in Australia

Dr Brandon Lui[1], *Dr Zille Khattak*[1], *Dr Anna Kwok*[1], *Dr Jeffrey Lai*[1], *Dr Prahlad Ho*[1], *Dr Hui Yin Lim*[1,2]
[1]*Northern Health, Epping, Australia,* [2]*The University of Melbourne, Parkville, Australia*

Aim: Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is increasingly recognised as a chronic disease with significant recurrence rates and resulting morbidity or mortality. The availability of direct oral anticoagulants (DOACs), listed by Pharmaceutical Benefits Scheme in 2013 in Australia, has changed the landscape of VTE management. We aim to characterise the real-world experience of VTE management in our study population.

Method: Retrospective evaluation of VTE events managed at Northern Health, Melbourne, Australia from January 2012 to June 2019 (median follow-up 5.6 years). The analysis included patient demographics, associated risk factors, management and outcomes.

Results: 2055 VTE events involving 1932 individuals (median age 65 years (range 16-102); 53% females) were analysed. These events included 1450 (71%) DVTs, 965 (47%) PEs and 360 (18%) with concurrent DVT/PE. 334 (16%) patients had active malignancy. 60% events (n=1233) were provoked with the most common provoking factor being injury/immobility (n=486, 24%) followed by surgery (n=344, 17%). 280 (14%) events occurred despite being on some form of anticoagulation. The median duration of anticoagulation was 6 months. 872 (42%) cases were managed with warfarin, 365 (18%) with enoxaparin and 673 (33%) with a DOAC. 220 (11%) patients experienced recurrent VTE while 75 patients (4%) experienced clinically significant major bleeding ($p<0.001$). Patients on warfarin and/or enoxaparin had higher rates of clinically significant major bleeding compared to DOACs (31/872 on warfarin (4%) vs 30/365 on enoxaparin (8%) vs 12/673 on DOAC (2%), $p<0.001$). Thrombosis and bleeding-related mortalities were comparable (30 (1.6%) vs 22 (1.1%), $p=0.26$). 68 patients (4%) were diagnosed with subsequent malignancies.

Conclusion: The recurrent thrombosis rate was 11% with a 4% rate of clinically significant major bleeding in this study. Bleeding rates were lower in patients treated with DOAC supporting the use of DOACs as first-line therapy in appropriately selected patients.

T021

A retrospective evaluation of the management of isolated distal deep vein thrombosis in Australia

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Aim: Isolated distal deep vein thrombosis (IDDVT) is often viewed to be of less clinical significance than major venous thromboembolism (VTE). However, studies report variable recurrence rate (2-19%) with significant heterogeneity in the IDDVT management. We aim to evaluate the characteristics of IDDVT in our study population.

Method: Retrospective evaluation of IDDVT events managed at Northern Health, Melbourne, Australia from January 2012 to June 2019 (median follow-up 5.7 years). Analysis included demographics, associated factors, management and outcomes.

Results: 429 patients (median age 63 years (range 18-102), 56% females) presented with 438 cases of IDDVT in this time period. The majority (297 cases, 68%) were provoked, most commonly due to injury/immobility (n=142, 33%) followed by surgery (n=116, 26%). Prior VTE history was present in 82 (19%) cases. Twenty-nine patients (7%) had active malignancy at time of diagnosis. The median duration of anticoagulation was 3 months for provoked events compared to 4 months for unprovoked events (p=0.015). Warfarin was the most common anticoagulant used (189 cases, 43%), followed by direct oral anticoagulants (DOACs) (152, 35%). DOACs were only listed by Pharmaceutical Benefits Scheme for use in Australia in 2013. There were 53 (12%) patients with recurrent VTE (including 18 (34%) as major VTE) and 9 (2%) patients with clinically significant major bleeding. An analysis of the overall database demonstrated that IDDVT patients had comparable VTE recurrence rate to those with major VTE (12% vs 11%, p=0.44) but lower major bleeding rates (2% vs 4%, p=0.036). There were four bleeding-related deaths (all on warfarin/enoxaparin), with no thrombosis-related deaths. Fourteen cases (3%) were diagnosed with subsequent malignancy.

Conclusion: The majority of IDDVT were provoked although the risk of recurrent thrombosis was comparable to major VTE despite a lower major bleeding rate. These data suggest that IDDVT is not always as benign as assumed.

T022

A retrospective evaluation of the management of venous thromboembolism in cancer patients

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Title: A retrospective evaluation of the management of venous thromboembolism in cancer patients

Aim: Cancer is a well-recognised risk factor for venous thromboembolism (VTE) with higher mortality. We aim to evaluate the characteristics of VTE in cancer patients in our study population.

Method: Retrospective evaluation of VTE events provoked by malignancy at Northern Health, Melbourne, Australia from January 2012 to July 2019 (median follow-up 5.4 years). Analysis included demographics, associated factors, management and outcomes. The outcomes of the cancer patients were compared to those without malignancy.

Results: 327 cancer patients presented with 346 (16.8%) VTE events out of a total 2055 VTE presentations, 224 (64.7%) events occurred in metastatic disease. This was compared to 1605 non-cancer patients who presented with 1709 VTE events - 51 of these individuals developed subsequent malignancy. Cancer patients were older (median age 71 vs 63 years, p<0.001) with a male predominance (57.2% vs 45.0%, p<0.001). Cancer patients were more likely to develop pulmonary embolism (56% vs 45%, p<0.001), above-knee deep vein thrombosis (DVT) (36% vs 18%, p<0.001) and bilateral DVT (13% vs 4%, p<0.001) compared to non-cancer patients. 231 patients with malignancy received indefinite anticoagulation; the majority (233, 67%) received enoxaparin; DOAC (39, 11%) was second most common and warfarin third (33, 10%). For those who had a limited period of anticoagulation due to cancer remission, the median duration of anticoagulation was 6 months. There were 26 recurrences (8%) in the malignant population despite 12 patients being on therapeutic anticoagulation, compared to 194 recurrences (13%) in the non-cancer patients of which only 29 of these patients were on therapeutic anticoagulation (46.2% vs 14.9%, p<0.001). All-cause mortality for cancer and non-cancer groups was 71% and 13% respectively (p=<0.001).

Conclusion: Cancer patients have higher clot burden and increased recurrence rate despite therapeutic anticoagulation. Further evaluation is required to optimise treatment in these patients.

T023

Efficacy and safety of valoctocogene roxaparvovec adeno-associated virus gene transfer for severe haemophilia A: results from the phase 3 GENEr8-1 trial

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Aim: Valoctocogene roxaparvovec is an AAV5-based gene therapy vector that transfers a B domain-deleted human factor VIII gene (FVIII-SQ) to hepatocytes. The aim of this study was to assess the efficacy and safety of valoctocogene roxaparvovec in people with severe haemophilia A.

Method: A phase 3, single-arm, open-label trial (GENEr8-1, NCT03370913) enrolled adult men with severe haemophilia A (FVIII ≤1 IU/dL) on FVIII prophylaxis negative for FVIII inhibitors. Participants received a single $6x10^{13}$ vg/kg valoctocogene roxaparvovec infusion. Primary endpoint was change from baseline in median FVIII activity (chromogenic assay) during weeks 49–52 in HIV-negative participants. Secondary endpoints were change from baseline in annualized treated bleed and FVIII infusion rates for participants rolling over from a noninterventional study. Adverse events (AEs) were monitored.

Results: Overall, 134 participants (median [range] age, 30 [18, 70] years) were dosed and completed 49–52 weeks. In 132 HIV-negative participants, chromogenic FVIII activity increased by a mean (95% CI)/median of 41.9 (34.1–49.7)/22.9 IU/dL at weeks 49–52. In 112 rollover participants, mean annualized bleeding and FVIII infusion rates decreased after week 4 by 84% and 99%, respectively, from baseline. After week 4, 89/112 (79.5%) participants experienced 0 treated bleeds vs 36/112 (32.1%) at baseline; 2/134 (1.5%) resumed prophylaxis. All 134 participants reported an AE; 22 (16.4%) reported serious AEs. Alanine aminotransferase elevations occurred in 115/134 (86%) participants; of these, 106 and 39 received corticosteroids and/or other immunosuppressants, respectively, per protocol, and 95.6% of events resolved. Other common AEs (≥30%) were headache (38%), nausea (37%), and aspartate aminotransferase elevation (35%). No participants developed FVIII inhibitors or thromboembolism. Additional data will be presented at BLOOD.

Conclusion: In the largest-to-date haemophilia gene therapy trial, valoctocogene roxaparvovec yielded meaningful endogenous FVIII expression in participants with severe haemophilia A, resulting in significant decreases in bleeding and FVIII infusion.

T024

Case report of vaccine induced thrombocytopenia and thrombosis (VITT) following ChAdOx1 Covid-19 vaccine and literature review of anti-Platelet Factor 4 antibodies assays in this syndrome

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Background & Aim: A rare syndrome of vaccine induced thrombocytopenia and thrombosis (VITT) has been reported post vaccination with both ChAdOX1 nCoV-19 (Oxford-Astrazeneca) and Ad26.COV2 vaccine (Johnson & Johnson). The syndrome bears clinical and pathophysiological resemblance to Heparin induced thrombocytopenia (HIT). Anti-Platelet Factor 4 (PF4) antibodies have been detected via a variety of enzyme linked immunoassays (ELISA) in nearly all reported cases. Unlike in HIT, rapid immunoassays assays based on chemiluminesence (CLIA), particle gel (PagiA) and lateral flow (LFIA) techniques have been mostly negative. The aim of this report is to (i) describe the laboratory features of a local case of VITT post ChAdOx1 and (ii) review the literature regarding use of rapid HIT immunoassays in VITT.

Case: A 59-year-old previously well man presented post ChAdOx1 vaccine with fevers, myalgias, headache and below knee deep venous thrombosis. Platelet nadir was 26 x10^9/L and D-Dimer >35 µg/mL. ELISA assay with Asserachrom HPIA (*Stago*) was positive with optical density (OD) of 3.25 (threshold 0.252). CLIA with HemosIL AcuSTAR HIT-IgG (Werfen) was negative at 0.15 U/mL (threshold 1.0 U/mL) and STic lateral flow assay (Stago) was negative. The patient was successfully treated with intravenous immunoglobulin (2g/kg in two divided doses) and therapeutic anticoagulation.

Literature Review: Published case reports, case series and retrospective studies regarding VITT associated with ChAdOX1 were reviewed and included if they reported the use of rapid immunoassays and/or ELISA. The observed pattern of discrepant results has been commonly reported in VITT. All types of rapid immunoassays perform poorly compared to ELISA in published series.

Conclusion: In conclusion, although rapid immunoassays are useful for HIT diagnosis, they should not be used in the diagnosis of VITT. The mechanism of this discrepancy is poorly understood and may be an important area of research for better understanding of VITT pathophysiology.

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T025

A retrospective analysis of the investigative practices of acute limb ischaemia presenting within an unknown aetiology

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Aim: Acute limb ischaemia (ALI) is a limb and life-threatening condition with significant morbidity**.** There are currently no consensus recommendations for the investigative practices to determine the aetiology of ALI presenting without a known aetiology. We undertook a detailed analysis of all investigations performed to identify an underlying precipitant in those with unexplained ALI and formulated a suggested diagnostic algorithm for the evaluation of unexplained ALI.

Method: ALI cases presenting to a tertiary referral centre over a 3-year period were reviewed, and known aetiologies, and investigations undertaken to determine the underlying aetiology of unexplained ALI were obtained.

Results: Most patients had a predisposing factor for ALI (195 of 222) at the time of clinical presentation. Of these 195 cases, the most common isolated precipitant was a history of significant peripheral arterial disease (n=106), followed by a known history of atrial fibrillation (n=31). Unexplained ALI was found in 27 of 222 patients (12%), of which 21 (78%) had a cause for ALI established after further investigations. Six patients had no cause identified despite extensive work-up. Most patients with unexplained ALI had a cardioembolic source identified as the underlying cause (62%), and this included atrial fibrillation, infective endocarditis, cardiac myxoma and intra-cardiac thrombus. Other causes of unexplained ALI were detected by computed tomography (CT) imaging and included newly diagnosed significant atherosclerotic disease (19%), embolism from isolated proximal large vessel thrombus (10%) and metastatic malignancy (10%). There were no cases attributed to inherited thrombophilias, myeloproliferative neoplasms or anti-phospholipid syndrome.

Conclusion: Among patients with unexplained ALI, the majority had a cardioembolic source highlighting the importance of comprehensive cardiac investigations. A subset of patients had alternative causes identified on CT imaging. These data support the use of a collaborative and integrative diagnostic algorithm in the evaluation of unexplained ALI.

T026

Low rates of venous thromboembolism in hospitalised COVID-19 patients: an Australian experience.

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Venous thromboembolic (VTE) complications appear common in hospitalised COVID-19 patients, particularly among critically ill patients in intensive care units. However, there is significant heterogeneity in the reported use of thromboprophylaxis. In response, our health service developed an institutional, risk-adapted thromboprophylaxis protocol for hospitalised COVID-19 patients.

Aims: The primary aim was to determine rates of symptomatic VTE in hospitalised COVID-19 patients. Secondary aims were to assess adherence to the institutional thromboprophylaxis guideline, and rates of bleeding complications.

Method: A retrospective, single-centre, cohort study was performed in consecutive hospitalised COVID-19 patients over a six-month period (March to August 2020). Enoxaparin was used as thromboprophylaxis in all patients without a contraindication, with dose adjusted according to disease severity, weight and renal function.

Results: Eighty-six patients were hospitalised with COVID-19 during the six-month study period. Median age was 77 years (range 25 to 97 years). Twenty-nine patients (34%) had mild disease, 35 patients (41%) had moderate disease, and 22 patients (25%) had severe/critical disease. No in-hospital VTEs were diagnosed. Eighty-one patients (94%) received anticoagulation, with 90% adherence to institutional thromboprophylaxis guidelines. Four bleeding events occurred, with one clinically relevant non-major bleeding event and three minor bleeding events.

Conclusion: Low rates of VTE were identified in hospitalised COVID-19 patients using a risk-adapted thromboprophylaxis protocol. Further prospective studies will help refine VTE risk and optimal thromboprophylaxis strategies in COVID-19 patients.

Pulmonary embolus in patients with COVID-19: an Australian perspective

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Whilst pulmonary embolus (PE) is known to occur in critically unwell patients who are hospitalised, data has emerged indicating that this risk may be higher in those hospitalised with coronavirus disease 2019 (COVID-19) and remains high in this group despite prophylactic anticoagulation[1].This is a retrospective analysis of 65 patients with COVID-19 hospitalised at a large Australian tertiary hospital (Austin Health) from March - August 2020 looking at the incidence of PE during admission and up to six months after discharge.

Results: Seventeen patients were admitted with non-severe COVID-19 and 88% received prophylactic anticoagulation or therapeutic anticoagulation for a pre-existing condition. None of these patients developed a PE during their index admission or at follow up.

Forty-eight patients were admitted with severe/critical COVID-19. Five patients (10%) developed PE. PE diagnosis occurred at a mean 21 days (+/-12.1) after COVID-19 diagnosis. All patients received standard inpatient thromboprophylaxis[2].

There was no difference in CRP at presentation in patients with severe/critical disease who went on to develop PE compared to those who did not (157.6 vs 111.4, p=0.37, CI 35.40–127.7).

However patients who developed PE had higher D-dimer at presentation than those with non-severe disease (4768 vs 1093, p=0.02, CI 5692–6781) and those with severe/critical disease who did not develop PE (4768 vs 1178, p=0.007, CI 850–6330). D-dimer was higher at the time of PE diagnosis compared with presentation though this did not reach statistical significance.

Conclusion: Corresponding with data from international studies the diagnosis of PE in a hospitalised cohort of patients with COVID-19 in Australia appeared to correlate with more severe disease and occurred despite the use of routine thromboprophylaxis. Further research into the aetiology of PE in critically unwell COVID-19 patients, optimisation of thromboprophylaxis and defining biological markers for those who may benefit from anticoagulation intensification is needed.

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T028

Interim analysis of a 24-month French, multicentre, prospective, non-interventional study evaluating the real-world usage and effectiveness of recombinant factor IX Fc fusion protein (rFIXFc) in people with haemophilia B (B-SURE)

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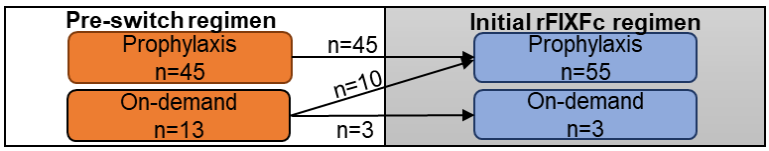
Aim: Safety and efficacy of rFIXFc were established in phase 3 trials in patients with severe haemophilia B (HB) showing low annualised bleeding rates (ABR) with 7 to ≥14 day prophylaxis dosing intervals. Since rFIXFc launch in France in 2018, the B-SURE study prospectively evaluates real-world effectiveness and usage of rFIXFc over 24 months. This is an interim analysis of patients with ≥9 months prospective observation from the ongoing B-SURE (NCT03655340) study.

Method: This interim analysis (data cut September 24, 2020) includes all patients with ≥1 follow-up visit after 9 months. ABR, dose and injection frequency with on-demand and prophylactic rFIXFc were described and compared to previous FIX therapy. Patient- and clinician-reported satisfaction with rFIXFc were evaluated.

Results: The interim analysis included 59 of 91 enrolled patients. Mean age was 31.1 years (range: 4–67, 13 patients <12 years). Patients had severe (n=54), moderate (n=3) or mild (n=2) HB. Figure 1 shows treatment regimens before and after rFIXFc initiation. At rFIXFc initiation, the prescribed injection frequencies in 56 patients on prophylaxis were every 7 days (n=41), every 10 days (n=7), >10 days (n=6) and other (n=2). Last documented dosing frequency was every 7 days (n=35), every 10 days (n=12), >10 days (n=8) and other (n=1). Median (range) follow-up since rFIXFc initiation was 22 (9.5–107.7) months. Data on ABR, injection frequency and factor consumption, before and after initiation of rFIXFc prophylaxis, are reported in Table 1. In patients on prophylaxis before and after rFIXFc initiation, the ABR on rFIXFc was low with reduced injection frequency compared to previous FIX treatment. Most physicians (92%) and patients (76%) were satisfied or highly satisfied with rFIXFc treatment at the latest assessment.

Conclusion: This interim analysis supports the effectiveness of rFIXFc prophylaxis in the real-world by maintaining a high protection from bleeds with a low injection frequency.

Figure 1. Treatment regimens before and after switch to rFIXFc*



*The figure includes patients with ≥3 months consecutive treatment on either prophylaxis or on-demand in the 6 months prior to rFIXFc initiation (n=58). Data on pre-switch regimen for one rFIXFc prophylaxis patient missing at data cut.

Table 1. Annualised bleeding rate, injection frequency and factor consumption, before and after initiation of rFIXFc prophylaxis

	Before/after rFIXFc initiation	Switch from FIX prophylaxis to rFIXFc prophylaxis, median (IQR)	Switch from FIX on-demand to rFIXFc prophylaxis, median (IQR)
ABR	before after	n=43; 2.0 (0.0–2.1) n=43; 0.6 (0.0–2.2)	n=9; 4.4 (0.0–8.1) n=9; 0.5 (0.0–0.6)
Joint ABR	before after	n=43; 0.0 (0.0–2.0) n=43; 0.0 (0.0–0.8)	n=9; 2.0 (0.0–8.1) n=9; 0.0 (0.0–0.6)
Annualised injection frequency	before after	n=38; 96.9 (60.2–106.7) n=38; 53.4 (45.0–58.0)	n=9; 10.9 (6.1–26.8) n=9; 29.5 (26.6–31.9)
Annualised rFIXFc consumption (IU/kg/year)	before after	n=38; 3491 (2629–4518) n=38; 3076 (2440–3408)	n=9; 421 (304–915) n=9; 1797 (1423–2307)

FIX, factor IX; rFIXFc, recombinant factor IX Fc fusion protein; IQR, interquartile range; ABR, annualised bleeding rate; IU, international unit.

T029

Real-world effectiveness and usage of recombinant factor IX Fc fusion protein (rFIXFc) for management of major/minor surgeries in patients with haemophilia B in France: results from the ongoing B-SURE study

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Aim: B-SURE (NCT03655340) is a 24-month prospective, observational study evaluating real-world effectiveness and usage of rFIXFc in patients with haemophilia B (HB). The aim is to describe rFIXFc use for management of major/minor surgeries performed in the B-SURE study.

Method: Ninety-one patients enrolled between Sep 2018–Sep 2019. This descriptive interim analysis included data collected up to Sep 30, 2020, in patients who underwent ≥1 surgical intervention receiving rFIXFc treatment. Major surgery was any procedure usually (not always) involving general anesthesia/respiratory assistance in which a major body cavity was penetrated/exposed. Minor surgery included all other surgeries. Patient monitoring/treatment during perioperative periods were according to routine practice.

Results: Ten major surgeries were performed in 9 patients with severe HB (median [range] age 44 [30–83] years): 9 orthopaedic (6 knee replacements, 2 arthroscopic synovectomies, 1 ankle arthrodesis) and 1 aortic valve replacement. All patients were hospitalised for a median (range) of 9 (7–38) days, and the median (range) rFIXFc consumption and number of injections per day was 47 (20–76) IU/kg/day and 1.0 (0.4–1.8), respectively. After discharge, rFIXFc (median [range] 15 [0–60] IU/kg/day and 0.3 [0–1] injections) was given for 16 (0–92) days.

Thirty-nine minor surgeries were performed in 26 patients (22 with severe HB); median (range) age was 37 (4–83) years. Common procedures included tooth extraction (10), orthopaedic (8), and gastrointestinal endoscopic (5) procedures. rFIXFc was used for surgical management, with a median (range) consumption of 65.9 (16.2–166.7) IU/kg/day and 1.0 (0.4–2.3) injections/day, during 2 (1–13) days.

One bleeding was reported 11 days after wisdom tooth removal that required additional rFIXFc treatment. No other bleedings were reported.

Conclusion: This interim analysis of a surgical series observed in the B-SURE study confirms that rFIXFc is well tolerated and efficacious when used perioperatively in HB patients

T030

Comprehensive evaluation of treatment and outcome for patients with Haemophilia A and Haemophilia B on extended half life (EHL) products: a 12-month data analysis

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Background: EHL recombinant factor VIII and IX products have been available in Australia since March 2018. Preliminary analysis of the Australian experience of switching to EHL demonstrated that extended half life products were associated with fewer injections, increased treatment adherence and improved bleeding outcomes compared to standard half life products.

Aim: To analyse EHL pharmacokinetic data and investigate the effectiveness of prescribed treatment regimen on bleed outcomes and correlation with pharmacokinetics.

Method: Demographic data was derived from the Australian Bleeding Disorder Registry (ABDR) for patients with Haemophilia A (HA) and Haemophilia B (HB) from whom consent had been obtained. Data was obtained on severity, age, product, date of commencement, treatment regimen, factor usage and bleeds. Pharmacokinetic data was obtained from the WAPPS-Hemo database.

Results: The complete EHL dataset for analysis including bleed and pharmacokinetic data constituted 115 HA and 59 HB patients. Median prescribed dose at EHL commencement was 47.9 IU/Kg (42.8-53.5) for HA and 51.5 IU/Kg (46.4-59.4) for HB patients. Following annual review there was very negligible shift in dosing paradigm, □-1.1 IU/Kg (-4.7-0.0) and □-1.6 IU/Kg (-4.4-0.0) for HA and HB patients respectively. Both HA and HB patients had a median of 0 (0-1) spontaneous bleeds with 62.6% (72/115) and 64.4% (38/59) reporting zero bleeds. Results of the Pearson Correlation test indicated that there was no significant association between spontaneous bleeds and pharmacokinetic measures (half-life hours, difference of dosing frequency hours and TimeTo5% hours), $r(115) = 0.19$, $p = 0.14$ in HA patients. However statistically significant but medium correlation was observed in HB patients, $r(59) = 0.58$, $p = 0.007$. Around 33% (7/21) of HB patients that reported spontaneous bleeds had their treatment regimen updated based on their pharmacokinetic measures.

Conclusion:
EHL pharmacokinetic data was very useful in understanding effectiveness of treatment and improving prescribing practices.

T031

Storage of apheresis platelets in lipaemic plasma affects aspects of platelet function and surface receptor expression

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Aim: Lipaemia in blood donations is usually due to a high fat meal prior to donating, metabolic disorders or medication. Whilst the effect of lipaemic plasma on red cell storage has been investigated, there is little data regarding the storage of platelets in lipaemic plasma. The aim was therefore to study the impact of storing platelets in lipaemic plasma.

Methods:

Double apheresis platelet components were pooled, centrifuged and resuspended in either control (non-lipaemic), moderately lipaemic plasma (n=5), or non-lipaemic and severely lipaemic plasma (n=6); all 70% SSP+/30% plasma. Plasma was visually assessed for extent of lipaemia based on opacity. Platelet concentrates were stored for 7 days at 20-24°C with agitation. Platelet metabolism, mitochondrial membrane polarisation, activation and function were measured on day 1, 5 and 7 of storage, using *in vitro* assays. Data were analysed using a two-way repeated measures ANOVA; $p<0.05$ was considered significant.

Results:
Storage of platelets in lipaemic plasma had no effect on platelet concentration or metabolism. Mitochondrial membrane depolarisation, measured using tetramethylrhodamine ethyl ester was significantly higher in platelets stored in either moderately ($p=0.001$) or severely lipaemic plasma ($p=0.037$). Lipaemic plasma had no effect on platelet activation, as evidenced by annexin-V binding, cell surface CD62P and release of soluble CD62P. However, CD62P following TRAP-6 stimulation was blunted in platelets stored in moderately and severely lipaemic plasma ($p=0.009$ and $p=0.002$ respectively). Storage in moderately and severely lipaemic plasma reduced surface levels of GPIb ($p=0.015$ and $p=0.008$) and GPVI ($p=0.027$ and $p=0.008$), while CD61 (GPIIIa) expression was significantly lower only in severely lipaemic plasma ($p=0.007$). Viscoelastic parameters (TEG) were not significantly different.

Conclusion: Storage of platelets in lipaemic plasma does not affect platelet metabolism, but differentially affects platelet receptor expression and their ability to respond to agonists. This may be reduce their efficacy upon transfusion, warranting further investigation.

T032

Overall Haemostatic Potential assay detects increased fibrin generation and reduced fibrinolysis potential in anticoagulated patients following venous thromboembolism

Dr Julie Wang[1,2], *A/Prof Prahlad Ho*[1,2]
[1]*Northern Health, Epping, Australia,* [2]*University of Melbourne, Parkville, Australia*

Aim: The Overall Haemostatic Potential Assay (OHP) is a global coagulation assay that can measure fibrin generation and fibrinolysis potential. Studies in VTE have been sparse. Our aim was to characterise fibrin generation and lysis potential in anticoagulated VTE patients using the OHP assay.

Method: Adult patients were recruited following a confirmed diagnosis of DVT and/or PE, and blood sampled whilst receiving therapeutic anticoagulation. Platelet poor plasma (PPP) was obtained and analysed by the OHP assay in which fibrin generation and fibrinolysis is measured spectrophotometrically at 405nm. The overall coagulation potential (OCP) is the area under the time-curve of PPP activated by thrombin. The OHP is determined by the addition of tPA (350ng/mL) and thrombin to a parallel plasma sample. The overall fibrinolysis potential (OFP) is calculated by .

Results: 208 patients were recruited from Jan 2018 to Jan 2021. Compared with normal control patients (previous data), study subjects displayed significantly higher OCP, OHP, and reduced OFP (Table 1). There were no significant differences between provoked/unprovoked or major/minor VTE. Patients with active malignancy, or those subsequently diagnosed with malignancy displayed significantly higher OHP and reduced OFP compared to those without malignancy (Table 1). Patients with residual PEs had significantly higher OCP and OHP compared with those without residual PEs. No differences were found according to presence of residual thrombus in those with DVT only. Patients receiving warfarin displayed significantly higher OCP and OHP compared to those treated with DOACs, which may be due to patient differences as displayed in Table 2.

Conclusion: High fibrin generation potential and reduced fibrinolysis potential were detected by OHP after acute VTE, despite being on anticoagulation. Individuals with malignancy, with residual PE and anticoagulated with warfarin had significantly hypercoagulable and/or hypofibrinolytic results. Further study is required to explore the utility of OHP in the VTE population.

Table 1 – OHP results of various sub-populations of VTE patients

	Normal control	**All subjects**	**p**	**Malignancy**	**No malignancy**	**p**	**PE/DVT with no residual PE**	**PE/DVT with residual PE**	**p**
No. results	143	208		17	189		74	13	
OCP	35.7	41.54	*<0.001*	46.61	41.33	*0.06*	39.65	47.92	*0.01*
OHP	7.3	11.28	*<0.001*	15.41	10.95	*0.002*	10.43	14.92	*0.02*
OFP%	80.1	73.62	*<0.001*	68.53	74.19	*0.01*	74.32	71.48	*0.28*

Table 2

	OCP, mean	**OHP, mean**	**OFP, mean**	**Age**	**Weight**	**D-dimer**	**F8**	**vWF Ag**	**Fibrinogen**
Warfarin N=37	48.09	13.08	73.87	55.9	113.27	0.44	196.06	199.74	4.4
DOACs N=155	39.84	10.49	74.2	56	89.18	0.56	146.97	145.09	3.6
p-value	*<0.001*	*0.006*	*0.82*	*0.96*	*<0.001*	*0.68*	*<0.001*	*<0.001*	*<0.001*

T033

Flow cytometry identifies an early stage of platelet apoptosis produced by agonists of the P2X1 and P2X7 receptors

Prof James Wiley

Aim: Strong evidence suggests that platelet lifespan is regulated by an intrinsic pathway of caspase enzymes but a possible role for extrinsic signals is unclear. Platelets express the P2X1 receptor and our data also show P2X7 expression. Activation of P2X7 is known to cause apoptosis in nucleated cells but the function of platelet P2X1 is unclear. Our aim was to study if P2X-receptor agonists could initiate platelet apoptosis.

Method: Platelet-rich plasma was first stained with MitoTracker Deep Red, then incubated at 37^0 for 10 min with BzATP (benzylbenzyl-ATP),a potent agonist of both P2X1 (at nanomolar concentration) and of P2X7 (at high micromolar concentration). The reaction tube was centrifuged to remove viable platelets and the cell-free supernatant stained with CD41 and analysed by flow cytometry on Cytoflex S. The MitoTracker+CD41+ particles formed a homogeneous population which were moderately AnnexinV+ and were enumerated as early stage apoptotic platelets. As a positive control , PRP was incubated with ABT737, known to induce apoptotic change of platelets via an intrinsic pathway associated with release of similar AnnexinV+ particles to the medium.

Results: A dose-dependent formation of apoptotic platelets was observed between 5 and 500 uM BzATP consistent with platelet P2X7 activation while a variable formation of apoptotic particles occurred at 100 – 200 nanomolar BzATP consistent with P2X1 activation in some but not all platelet donors. Production of apoptotic platelets also occurred with the P2X1-selective αβ-meATP agonist. Formation of apoptotic platelets by either 100 nM or by 0.5 mM BzATP was inhibited by preincubation of platelets with latruculin A, an inhibitor of the actin cytoskeleton or by methyl-beta-Cyclodextrin, which removes cholesterol from lipid rafts.

Conclusion : Our data shows functional P2X1 and P2X7 receptors are localised in platelet lipid rafts where P2X-agonists even at nanomolar levels can produce early stage apoptotic platelets in human blood.

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N001 – N009: Nurses Posters

N001

Improving care for thalassaemia patients in line with best practice standards at a tertiary referral cancer care centre

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Background: Beta-thalassaemia major is a chronic haematological disorder that requires life-long management. This project aimed to improve thalassaemia patients' care through the implementation of best practice standards at a tertiary referral cancer care centre.

Methods: This project utilised a clinical audit design. A pre-and post-implementation audit was carried out following best practice standards for patients with thalassaemia. Chart review of nine thalassaemia patients was undertaken pre-and post-implementation of staff education, local clinical guidelines, and an annual care plan to manage thalassaemia to determine adherence to best practice standards. Data were collected between June 2019 and June 2020 at a specialist outpatient and day treatment unit located in inner Brisbane, Australia.

Results: The pre-implementation audit results showed low compliance to the audit criteria, with the exception of nursing staff education. Following the implementation of strategies to align current care with evidence-based recommendations, the post-implementation audit showed improvement across all areas. Overall, implementation strategies were successful in improving patient care for thalassaemia patients by 100%. Staff thalassemia education increased from 45% to 92%.

Conclusion: Implementing an individualised treatment plan and thalassaemia-specific nursing documentation as well as developing local clinical guidelines and providing targeted nurse education were effective strategies to improve care for thalassaemia patients in line with best-practice standards.

N002

Using a CADD is not a fad

Ms Jo Cryer[1]
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Several chemotherapy protocols have traditionally been administered in the inpatient setting e.g. BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning chemotherapy for autologous transplant, HIDAC (high dose cytarabine) for acute myeloid leukaemia consolidation chemotherapy and DA-R-EPOCH (dose adjusted rituximab, etoposide, vincristine, doxorubicin, prednisolone and cyclophosphamide).

Enabling patients to spend more time at home improves overall wellbeing and improves quality of life. Being treated in an outpatient setting ensures timely administration of chemotherapy.

Competing demands for inpatient beds can lead to treatment delays. To ensure timely chemotherapy administration and more patient freedom a new method of administration for these chemotherapy protocols had to be investigated and implemented.

This poster will describe how our institution implemented the change in practise.

N003

Nurse-led ultrasound guided IV cannulation: Improving apheresis and the patient experience

Ms Anna Duncan[1], *Dr Anthea Greenway[1], Dr Amanda Walker[1], Dr David Metz[1], Ms Zoe Millard[1], Mr Brendan Cusack[1]*
[1]The Royal Children's Hospital, Parkville, Australia

Aim: To determine the impact of nurse-led Point of Care Ultrasound (POCUS) guided IV cannulation for apheresis procedures in children with sickle cell disease by identifying if POCUS can improve the apheresis experience for our patients. In addition, whether the nurse-led POCUS program reduced Anaesthetic Vascular Access Service (AVAS) referrals and the need for surgically implanted Central Vascular Access Devices (CVADs).

Method: Data was obtained retrospectively from the medical records of all children at the Royal Children's Hospital currently on the chronic red cell exchange (RCE) program (N=9).

Data for one patient was examined: number of cannulation attempts, whether AVAS referral was required, overall length of stay, the number of aborted procedures due to inadequate IV access and delay from time of admission to procedure start time prior to and following POCUS were considered.

Results: Since implementing nurse-led POCUS IV cannulation in the apheresis unit in 2018, patients relying on cannulation from AVAS have reduced substantially. The case study demonstrated a reduction in delay to procedure start time, shorter overall admission time, fewer alarms and aborted procedures and unsuccessful cannulation attempts.

5 patients successfully avoided the need for CVADs due to ongoing successful nurse-led POCUS IV cannulation while 2 patients subsequently required a CVAD.

All patients and families reported improvement in their apheresis experience since the introduction of nurse-led POCUS IV cannulation.

Conclusion: Nurse-led POCUS is beneficial for paediatric SCD patients requiring frequent cannulation for chronic RCE procedures. The case study suggests that training apheresis nursing staff in POCUS IV cannulation can significantly improve the overall patient experience by reducing the number of cannulation attempts and shortening the length of stay for each admission. Surgical insertion of CVADs have been avoided in 55% of the chronic RBCE cohort at RCH. Our results indicate that nurse-led POCUS cannulation can have positive outcomes for children with SCD who require apheresis procedures for management of their severe chronic disorder.

N004

Standard versUs peRForated peripheral intravenous catheter (SURF): a pilot randomised controlled trial preliminary findings

Dr Nicole Gavin[1,2,3], *Ms Elizabeth Wignall[4], Dr Nicole Marsh[1,3,5], Dr Louise Marquart[6], Ms Catherine O'Brien[4,5], Dr Anthony Verderosa[7], Dr Makrina Totsika[7], Dr Karen Dobeli[4], Dr Samantha Keogh[1,3,5]*
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Aim: To evaluate the effectiveness of perforated peripheral intravenous catheters (PIVCs) compared to standard PIVCs in reducing PIVC failure during injection for contrast enhanced computed tomography scans.

Method: A single centre, parallel-group, pilot randomised controlled trial (RCT) conducted between 30th March and 27th May 2020. Adult participants diagnosed with cancer were assigned to a non-perforated PIVC (standard care) or a PIVC with a novel perforated design (intervention) for the administration of intravenous contrast. There were two primary outcomes: (1) feasibility of an adequately powered RCT with pre-established criteria for eligibility, recruitment, protocol adherence and retention and (2) all cause PIVC failure. Secondary outcomes included: first insertion success, modes of PIVC failure, PIVC dwell time, contrast injection parameters (volume and injection rate), CECT image quality, radiographer satisfaction and adverse events, such as contrast reaction and extravasation, was also monitored.

Results: Feasibility outcomes were met, except for eligibility (≥80%) and recruitment (≥80%). In total, 166 participants were screened, 128 (77%) were eligible, and of these 101/128 (79%) were randomised; 50 to standard care and 51 to the intervention. There was no missing data. No patients withdrew from the study; however, the desired contrast injection rate was not achieved in 4/101 (4%) of participants; 2 from each group. One participant in the intervention received an extravasation injury. Radiographers were very happy (rated the quality 10/10 on a 0-10 Likert scale) with flow rate (42/50; 86% in the standard care and 45/51; 88% in the intervention) and the image quality (42/51; 86% in the standard care and 43/50; 84% in the intervention). The median PIVC dwell time was 37 minutes.

Conclusion: This pilot RCT suggests perforated PIVCs provide expected flow rate and similar image quality to non-perforated PIVCs. Feasibility of conducting an equivalence RCT was demonstrated.

N006

Assessing Pentamidine usage as Pneumocystis jiroveci prophylaxis in a large Australian tertiary hospital

Ms Melissa Jensen[1]
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Aim: Trimethoprim-sulfamethoxazole (Co-trimoxazole) is the traditional first-line prophylactic agent used against *Pneumocystis jiroveci.* Used due to superior efficacy, spectrum of activity, low cost and ease of access [1,2,3]. Nebulised pentamidine can be utilised as an alternative prophylactic agent in patients with known cotrimoxazole allergies and post haematopoietic stem cell transplant (HSCT) patients with cytopenias [3]. The aim of this study was to evaluate the rationale for pentamidine usage within the HSCT population at a large tertiary Australian hospital.

Method: This study involved a retrospective audit investigating patients who received pentamidine over a three-month period. Patients were identified utilising medical records and dispensing histories. Data collected included, known allergies (& severity), full blood count at time of dose, number of doses received, type/date of HSCT, presence of graft versus host disease (GVHD) & current immunosuppressive regimen.

Results: Seventeen patients were identified as HSCT patients, two patients were excluded due to trial participation and transplant received at another site.

Pentamidine was regularly received in eleven patients. Ten of these patients had a documented trimethoprim +/or sulfamethoxazole allergy recorded; in five patients the severity of allergy was documented and for four patient's de-sensitization (either to occur or had occurred) was documented.

Seven patients had been receiving Pentamidine regularly for greater than one year with four of these patients requiring immunosuppressive therapy for GVHD. Duration of treatment less than one year were proceeding per protocol or undergoing treatment for GVHD.

One patient regularly receives pentamidine doses with an unclear indication, no known allergies and no reference to full blood count.

Four patients received once off doses due to decreased platelet count/slow platelet engraftment post transplant.

Conclusion: Anti-biotic desensitization and PJP prophylaxis remaining in patients without immunosuppressants are potential target areas for further drug use optimisation. Further study is required to identify prescribing habits/rationale and influencing traits.

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N007

Platelet Clumping and Clotting: Identifying risk factors and management of anticoagulation during cMNC procedure

Zoe Millard[1], *Anna Duncan*[1], *Brendan Cusack*[1], *Amanda Walker*[1], *David Metz*[1], *Jacqueline Fleming*[1], *Anthea Greenway*[1]
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Aim: Multiple episodes of platelet clumping within the extracorporeal circuit were encountered soon after introducing the Continuous mononuclear cell (cMNC) procedure using Terumo Spectra Optia at The Royal Children's Hospital (RCH) in 2019. 3 out of the first 6 cMNC procedures ended in abandonment of procedure due to clotting of the circuit and prompted a review.

Method: Retrospective case reviews were completed, along with a root cause analysis performed by Terumo BCT, literature review and discussion with treating medical teams at RCH.

Patient characteristics were evaluated to identify clinical risk factors which may have contributed. Optia procedure data logs were analysed in conjunction with nursing procedure reports.

Results: Procedure logs highlighted multiple pauses to flow may have contributed to clumping/clotting. Nursing notes suggested vascular access difficulties was a contributing factor in the paediatric patient population.

Other risk factors identified were high peripheral leukaemia blast count at time of procedure and oestrogen stimulation for egg harvest prior to Peripheral Blood Stem Cell collection. Following discussion with Terumo BCT, AC ramping (lower initial Inlet:AC ratio until interface established) was introduced.

A further 64 cMNC procedures have since been completed. 7 children identified as at risk received AC ramping. Only three further episodes of circuit occlusion occurred. Thus, following a change in practice after 50% of procedures were aborted, only 5% were aborted in the subsequent 64 procedures, a highly significant improvement.

Conclusion: Identified risk factors of clumping and aborted procedure during cMNC collection may be part mitigated by initial adjustment of anticoagulation (AC ramping). Additionally, ensuring good vascular access is crucial to successful collection, particularly in younger children.
Substantial improvement in uneventful cMNC collections was seen after practice review and targeted use of AC ramping.
Further research into individual patient factors which may predict difficulty with collections would be beneficial to inform strategies such as AC ramping which may enhance likelihood of a successful cMNC collection free of complications.

Higher EQ-5D-5L utility scores at diagnosis are associated with improved overall survival in Australian patients with multiple myeloma: results from the Australian and New Zealand Myeloma and Related Diseases Registry

Dr Elizabeth Moore[1], *Dr Cameron Wellard[1], Dr Adam Irving[1], Associate Professor Zoe McQuilten[1], Professor Andrew Spencer[1], Professor Erica Wood[1]*
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Aim: Multiple myeloma (MM) is an incurable blood cancer with high disease burden. Early assessment of health-related quality of life (HRQOL) can help guide therapy planning. EQ-5D-5L (EQ5D) scores are collected in the Australian & New Zealand Myeloma & Related Diseases Registry (MRDR) at diagnosis and follow-up. We describe use of EQ5D utility scores to assess patients' HRQOL at diagnosis.

Method: Utility scores are a measure of HRQOL, from '0' (equal to death) to '1' (full health). Scores were calculated for Australian patients with EQ5D data at diagnosis on the MRDR (Feb 2013 - Mar 2021) using an Australian scoring algorithm[1]**.** Kaplan-Meier methods were used for survival analysis.

Results: Of 2239 Australian MRDR patients with MM, 483 had baseline EQ5D within 6m of diagnosis and data for all 5 dimensions. Median age was 68y (59-76), 63% were male, and median overall survival (OS) was 63m (54.1-NR). Figure 1 summarises EQ5D results at baseline. Patient characteristics were compared between EQ5D utility score groups (Q1: <0.25, Q2: 0.25-0.49, Q3: 0.50-0.74, Q4: 0.75-1.0) with no difference in median age, gender or disease stage (ISS) between the 4 groups (p≥0.19). As expected, with increasing utility score (better health), median EQ VAS score (patient-identified health status, 0 to 100, 100=best health, 0=worst) increased, and proportion of patients with ECOG performance status 2-4 (unable to work) decreased (p<0.001). Presence of cardiac disease decreased with higher utility score (p=0.048). Notably, higher utility scores at diagnosis were associated with improved OS (Figure 2, p=0.001).

Conclusion: EQ5D utility scores in Australian MRDR patients with MM were independent of age, gender and ISS=3, but high scores were associated with higher EQ VAS score, improved ECOG, less cardiac disease, and better OS. HRQOL of MM patients at diagnosis has prognostic potential with better EQ5D utility scores associated with longer OS.

Figure 1. Results of EQ5D at diagnosis. Each patient health dimension across the bottom of the graph, is scored on a five-point scale of increasing problems.

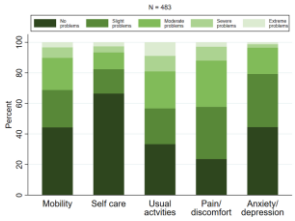
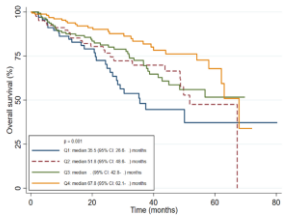


Figure 2. Overall survival for MM by utility score groups for EQ5D at diagnosis



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N009

Developing a national information and support group program for the carers of people living with myeloma.

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Aim: Myeloma Australia's support services have always been available to carers of people living with myeloma. However, we recognised a need to offer a space just for carers to help them cope with the unique issues of a complex disease, treatment side effects, supportive care needs and the impact of each relapse of their loved one.

The aim of this project was to understand the needs of carers in the Australian myeloma community to guide development of an appropriate carer-specific national information and support group program.

Method: A 14-question survey was emailed to the Myeloma Australia national database to gauge carer interest, priorities and needs. Four pilot information and support groups were held online in two Australian states over a two month period. Each group was facilitated by two myeloma support nurses. Attendees and facilitators evaluated sessions according to content, time of day and length of meeting. Data collection from the survey, feedback from pilot group attendees and a literature review were interpreted using thematic analysis to guide the program development.

Results: 144 survey responses were received in which 70% expressed interest in attending an information and support group. 17 carers and 6 facilitators evaluated the four pilot online information and support groups. Carers identified feelings of loneliness, helplessness, worry and exhaustion in the survey. Themes emergent from carer engagement in the study and review of local and international literature included priorities of gaining knowledge, developing coping strategies and the desire to share with others in a similar situation.

Conclusion: There are significant, unmet needs for carers of myeloma patients. Myeloma Australia has now launched carer information and support groups in all states. Future directions include development of resources for carers of people living with myeloma in Australia and collaboration with external organisations to expand national carer service provision

B001 – B004: BMTSAA Posters

B001

A pathogen specific T-cell bank generated by activation-induced CD137 selection

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Background: Immune reconstitution via adoptive transfer of pathogen specific T-cells (PSTs) can control viral infection in immune suppressed patients. We have developed a GMP compliant method for manufacture of enriched PST cell products for important opportunistic infections.

Method: HPC-A samples from healthy donors were stimulated with peptide pools of proteins from cytomegalovirus (CMV), Epstein-Barr virus (EBV), adenovirus (AdV) and aspergillus fumigatus (AF) resulting in activation-induced surface expression of CD137. Positive selection of $CD137^+$ cells was performed 16-24 hours post antigen stimulation. These were combined with irradiated $CD137^{neg}$ cells as feeder cells in a G-Rex®-6 device in media supplemented with cytokines IL-2, -7 and -15. Cultures were incubated for a total of 11 days.

Results: 47 T-cell products were generated specific for CMV (12), EBV (20), AdV (5) and multi-pathogen (CMV, EBV and AF; n=10). Product characteristics are summarised in Table 1.

Table 1: Characteristics of manufactured PST products (mean % values shown):

	$CD3^+CD137^+$ frequency (day 1)	**Fold-expansion (day 11)**	**$CD3^+$ % (in final product)**	**effector memory (% $CD3^+$)**	**central memory (% $CD3^+$)**	**Post-thaw viability**
CMV	0.20	2374	97.3	68.1	28.5	84.2
EBV	0.12	3322	98.3	71.9	24.5	85.7
AdV	0.09	2750	96.9	50.9	41.7	84.5
multi-pathogen	0.11 (CMV) 0.06 (EBV) 0.03 (AF)	7786 (CMV) 8365 (EBV) 16066 (AF)	95.7 *(combined multi-pathogen PST product)*	44.9	50.5	85.4

Antigen specific responses (measured by CD107a/b mobilisation and IFN-γ/TNF-α secretion) are shown in Table 2. HLA restricted responses were present in 11/12 CMV-, 20/20 EBV- and 5/5 AdV-specific products. CMV responses were confirmed using tetramers for HLA-A*02:01 (mean 65.6%), A*24:02 (7.7%), B*07:02 (21.3%) and B*35:01 (5.4%).

Table 2: Mean antigen specific responses in PST products (% of $CD3^+$):

	single pathogen PST products			***multi-pathogen PST products***		
	CMV	**EBV**	**AdV**	**CMV**	**EBV**	**AF**
CD107a/b$^+$	51.6	67.1	18.1	16.6	23.9	1.8
IFN-γ$^+$	32.6	47.0	35.3	12.2	15.5	2.2
TNF-α$^+$	27.2	41.9	35.2	12.3	16.1	4.2

Conclusion: We generated a cell bank of CMV, EBV, AdV and multi-pathogen-specific T-cells, using a rapid manufacturing protocol that resulted in highly enriched T-cell products. Products from the cell bank are being utilised in several clinical trials of adoptive immunotherapy.

B002

Targeted Recruitment of Unrelated Blood Stem Cell Donors in Western Australia

Carly Olsen[1]

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Background – The Western Australian Department of Health (the Department) have a state level agreement with Australian Red Cross Lifeblood (Lifeblood) to recruit and register unrelated stem cell donors onto the Australian Bone Marrow Donor Registry (ABMDR). With increasing national demand for younger aged, male donors of wider ethnic diversity, the Department and Lifeblood committed in 2016 to additional key performance indicators (KPIs) focused upon recruitment of 'targeted' donors.

Aim – To demonstrate the trends of Western Australia (WA) donor recruitment following the establishment of specific and targeted donor KPIs.

Method – Lifeblood provided the Department with 6 monthly summary reports including specific KPIs for targeted donors including: the proportion of ethnically diverse donors, male donors and 'ideal donors' (male donors between the ages of 18 and 35 years). This data has been analysed and presented alongside national data summarised within ABMDR Annual Reports.[1]

Results – Overall, the total number of WA based donors recruited to the ABMDR remains high, with WA representing 28.8% of new donors registered annually with the ABMDR since 2016.[1-4] Since 2016, the number of ethnically diverse new donors recruited each year in WA has significantly exceeded national and whole of registry percentages. [1] (Figure 1)

The percentage of newly recruited 'ideal' donors in WA has also exceeded national and whole of registry percentages. In 2019/20, 'ideal' donors represented 33% of newly recruited donors in WA. (Figure 2)

Conclusions – Overall, the introduction of KPIs for the recruitment of 'targeted' donors has resulted in an improvement in the ethnic diversity, sex and age profile of new donors. The benefit of this project has been an increase in the potential suitability of new donors to the Australian Bone Marrow Donor Registry and aligns better with contemporary domestic Australian needs.

References

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B003

Evaluation of Sysmex XN-series haemopoietic progenitor cell counts in determining the optimal timing of peripheral blood haemopoietic stem cell collection via apheresis

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Aim: Flow cytometric enumeration of CD34-positive cells in peripheral blood (PB) is the gold standard for determining when apheresis should commence during haemopoietic progenitor cell (HPC) mobilisation. Sysmex XN-series haematology analysers now have an automated module to quantify HPCs in PB. This study aimed to evaluate the utility of Sysmex XN-HPC counts in determining when mobilised patients and donors should commence apheresis.

Method: XN-HPC and flow CD34 counts were compared in a total of 66 paired PB samples using the Wilcoxon matched pairs test, Pearson's correlation and Passing-Bablok regression analysis. Receiver operator characteristic (ROC) curves were used to determine whether XN-HPC results could successfully identify individuals who were ready to commence apheresis, as defined as those with PB flow CD34 counts ≥20/µL. Excel Analyse-IT was used for statistical analysis.

Results: Although strongly correlated (Pearson's correlation, r-value=0.89), PB XN-HPC counts were found to be significantly higher than their paired CD34 counterparts, as demonstrated by the Wilcoxon matched pairs test (p<0.05) and Passing-Bablok regression analysis (constant bias or intercept of 8.72/µL, 95% CI for intercept: 1.42–12.55/µL).

ROC curve analysis was used to evaluate whether XN-HPC results could identify patients who were ready to commence apheresis. In order to eliminate all false positives, an XN-HPC cut-off of >91/µL was required, which correctly identified 5 out of 40 patients who were eligible to commence apheresis (specificity 100%, sensitivity 12.5%). Lowering the XN-HPC threshold below this allows more true-positive patients to be identified, however also results in the inclusion of false-positives. This is not clinically acceptable as any false-positives would result in an unwarranted apheresis procedure.

Conclusion:
XN-HPC and CD34 counts do not provide equivalent measures of HPCs in PB. Further data collection is required to determine appropriate XN-HPC cut-off values which are associated with sufficient clinical sensitivity and specificity. It is unclear whether the XN-HPC results could be used as a reliable clinical tool in identifying mobilised patients who are ready to commence apheresis for the harvest of PB-HPCs.

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Plerixafor in autologous collection:What time is now?

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Aim: To assess the effects timing of Plerixafor inclusion into mobilisation regimes on the quantity and quality of autologous haematopoietic stem cell collections (HPC).

Method: A retrospective analysis of 385 patients undergoing autologous HSC by apheresis, HSC(A), between 2011-2020 at the Calvary Mater Newcastle.

Patients were assessed for the inclusion of Plerixafor into the mobilisation regime, whether it was upfront, day (D) 2, or day (D) 3 of collection. Assessment was both within their group and as a whole for pre and post dosing differences in peripheral blood CD34% (PB CD34%) and CD34/µL, white cell counts (WCC), and collection volume. Number of collection required to meet their target was also included. Statistical significance was determined using Pearson correlation (weak, moderate, strong) and by two-tailed T-test (*P<0.05*) using Excel.

Results:

	Upfront	D2	D3	No Plerixafor
Number	54	54	6	267
Collections (mean)	1.83	2.22	3.5	1.55

381 patients were included (4 excluded due to incomplete data); Patients that received Plerixafor on D2 had a trend (*P=0.07*) towards a higher WCC post Plerixafor but no increase in their PB CD34%. Upfront Plerixafor group had a significant (*P=<0.05*) increase in PB CD34% with less increase in their PB WCC as compared to D2. In the upfront Plerixafor group, 41% only required 1 collection.

Those patients in the D3 group did not perform as well, but Plerixafor did significantly (*P=<0.05)* increase their PB CD34 and the CD34/Kg collected post dosing.

Conclusion: The PBS has strict guidelines for the administration of Plerixafor. CD34 collection is a costly procedure, both in consumables and staffing. Greater flexibility in assessing for those patients that could just have 1 collection because of incorporating Plerixafor as standard in their mobilisation regime, we believe would lead to significant cost savings in terms of staffing and consumables.