1

Cardio-oncology – what is it?

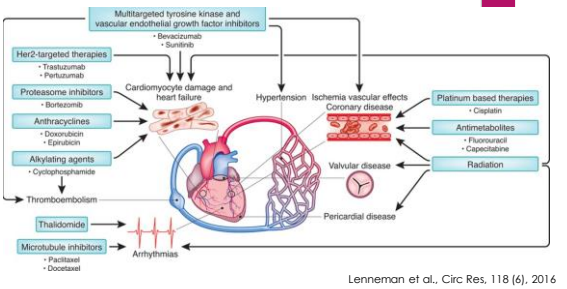
- Cardiac disease is second highest reason for mortality after recurrent malignancy in cancer survivors
- Cardio-oncology
  - to prevent patients with cancer developing heart problems caused by cancer treatments
  - to treat patients with cancer/treated for cancer who have developed heart problems as a result of their treatment

2

How can an oncologist break hearts!?

- Heart failure
- Acute myocarditis
- Cardiac ischaemia
- Systemic hypertension
- Pulmonary hypertension
- Pericardial diseases
- Thromboembolism
- QTc prolongation
- Arrhythmias

3



Lenneman et al., Circ Res, 118 (6), 2016

4

Heart failure

- Anthracyclines e.g. doxorubicin
- Anti-her-2 targeted therapy e.g. trastuzumab (Herceptin)
- Alkylating agents e.g. ifosfamide
- Anti-VEGF pathway signalling e.g. bevacizumab (Avastin)
- Proteasome inhibitors e.g. bortezomib

5

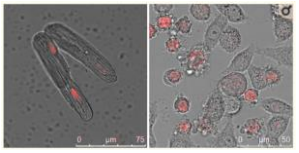
Heart failure – what oncologists do

- Baseline risk assessment
  - CV risk factor management including diabetes and hypertension
  - Ejection fraction assessment
    - Avoid heart failure inducing agents in those already in heart failure!
  - Patient discussion
    - Palliative vs adjuvant therapy
    - Acceptable risk/benefit

6

Heart failure – what oncologists do

- Mechanism anthracycline cardiotoxicity

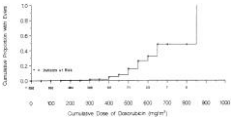


courtesy Dr. I Piotrowska

7

Heart failure – what oncologists do

- Prevention anthracycline cardiotoxicity
  - Select non-anthracycline regimen if possible
  - Limit dose of anthracycline
  - Continuous infusion (>6 hours vs <2 hours)
    - Lowers Cmax but not AUC
    - decreased rates clinical HF in adults
  - Dexrazoxane
    - Not medsafe licenced
    - Requires NPPA

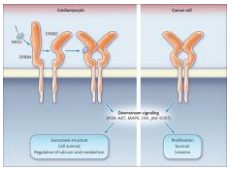


Swain et al., Cancer, 2003.

8

Heart failure – what oncologists do

- Mechanism trastuzumab cardiotoxicity



Cote et al., NEJM, 2012.

9

Heart failure – what oncologists do

- Prevention trastuzumab cardiotoxicity
  - Avoid co-administration with anthracyclines
    - Rates of NYHA class III/IV HF or death
    - BCIRG-006 (Slamon et al., NEJM; 365 (14), 2011)
      - **Anthracycline** (no trastuzumab) – **0.7%**
      - Sequential **Anthracyline** followed by **trastuzumab – 2%**
      - **Trastzumab** (no anthracycline) – **0.4%**
    - Concurrent **anthracyline/trastuzumab – 27%**
      - (Slamon et al., NEJM; 344 (11), 2001)

10

Heart failure – what cardiologists do

- Baseline risk assessment
  - CV risk factor management including diabetes and hypertension
    - HELP please
  - Ejection fraction assessment
    - Modality??
      - Echo vs MUGA vs MRI
      - Ideal modality
        - Reproducible
        - Low radiation exposure
        - Accessible at high frequency – greater than 3 monthly while on treatment
        - Picks up pre-clinical potentially reversible issues

11

Heart failure – what cardiologists do

- Speckle-tracking echo
  - Quantitative assessment of cardiac deformation
  - LVEF fall is late event ?? Too late
  - Early heads up
    - Modify anti-cancer therapy
    - Supportive cardiac therapy
    - Prevent progression to LVEF fall ???

12

Heart failure – what cardiologists do

- Speckle-tracking echo
  - Fallah-Rad et al. (J Am Coll Cardiol; 57, 2011)
    - Women prospectively monitored during anthracyline/trastuzumab sequential therapy
    - Cardiomyopathy in 24%
      - Definition - decline in LVEF >10%, below 55%, with sign/symptoms of CHF

13

Echocardiographic Variables	Normal (n = 32)	CM (n = 10)	p Value
LV dimensions			
LVEF			
Baseline	62 ± 5	64 ± 3	0.31
3 months	60 ± 8	58 ± 4	0.69
6 months	64 ± 4	42 ± 9 * †	<0.001
9 months	65 ± 4	39 ± 5 * †	<0.001
12 months	61 ± 9	49 ± 4 * †	<0.001

TnT, CRP, BNP NOT helpful

2D speckle tracking
- longitudinal and radial strain decreased at 3 months in ALL patients who went on to develop CM

NB LVEF didn't fall until 3 months later

2D speckle tracking			
Peak global longitudinal strain			
Baseline	−20.2 ± 2.4	−19.8 ± 1.8	0.72
3 months	−19.9 ± 2.3	−16.4 ± 1.1 * †	<0.001
6 months	−19.4 ± 2.8	−15.4 ± 1.8 * †	<0.001
9 months	−20.1 ± 1.7	−12.4 ± 2.1 * †	<0.001
12 months	−19.8 ± 1.9	−15.9 ± 2.7 * †	<0.001
Peak global radial strain			
Baseline	40.1 ± 11.1	41.4 ± 10.5	0.57
3 months	42.4 ± 13.2	34.5 ± 15.2 * †	<0.001
6 months	41.3 ± 15.4	30.5 ± 16.5 * †	<0.001
9 months	40.4 ± 15.2	29.4 ± 12.3 * †	<0.001
12 months	44.5 ± 17.2	33.4 ± 16.4 * †	<0.001

14

Characteristics	Normal (n = 32)	CM (n = 10)	Total Population (n = 42)	p Value
Age (yrs)	46 ± 8	47 ± 10	47 ± 9	0.48
BMI (kg/m²)	26 ± 5	25 ± 6	25 ± 7	0.90
CV risk factors				
Hypertension	4 (13)	1 (10)	5 (12)	1.00
Diabetes	4 (13)	2 (20)	6 (14)	0.62
Hyperlipidemia	12 (38)	3 (30)	15 (36)	1.00
Smoking history	2 (6)	2 (20)	7 (17)	0.24
Family history of CAD	4 (13)	3 (30)	12 (29)	0.33
Location of Ca				
Right	19 (59)	6 (60)	25 (60)	1.00
Left	11 (34)	4 (40)	15 (39.5)	1.00
Bilateral	2 (2.6)	0 (0)	2 (2.0)	1.00
Size of Ca (cm)	3.0 ± 2.0	3.2 ± 1.4	3.1 ± 1.7	0.83
Radiation	31 (97)	10 (100)	41 (98)	1.00
Lymph node +	19 (58)	5 (50)	24 (57)	0.72
Chemotherapy				
FEC	29 (91)	8 (80)	37 (88)	0.58
AC	3 (7)	2 (20)	5 (12)	0.58

15

Heart failure – what cardiologists do

- Prophylaxis medication
- Gulati et al., Eur Heart J.; 37(21), 2016
  - PRADA - a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol
  - Overall decline in LVEF was
    - 2.6 (95% CI 1.5, 3.8) percentage points in the placebo group
    - 0.8 (95% CI −0.4, 1.9) in the candesartan group
      - (P-value for between-group difference: 0.026).
    - No effect of metoprolol on the overall decline in LVEF was observed.

16

Heart failure – what cardiologists do

- Prophylaxis medication
- Pituskin et al., JCO; 35(8), 2017
  - MANTICORE 101–Breast
  - HER2-positive early breast cancer on adjuvant trastuzumab
  - perindopril, bisoprolol, or placebo (1:1:1)
  - After 17 cycles of trastuzumab
    - indexed left ventricular end diastolic volume increased
      - perindopril (+7 ± 14 mL/m²),
      - bisoprolol (+8 mL ± 9 mL/m²),
      - placebo (+4 ± 11 mL/m²; P = .36)

17

Heart failure – what cardiologists do

- Prophylaxis medication
- Pituskin et al., JCO; 35(8), 2017
  - MANTICORE 101–Breast
  - HER2-positive early breast cancer on adjuvant trastuzumab
  - perindopril, bisoprolol, or placebo (1:1:1)
  - After 17 cycles of trastuzumab
    - trastuzumab-mediated decline in LVEF
      - bisoprolol-treated patients (−1 ± 5%)
      - perindopril–treated patients (−3 ± 4%)
      - Placebo-treated patients (−5 ± 5%) groups (P = .001).

18

Heart failure – what cardiologists do

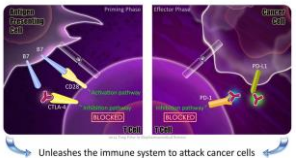
- Cessation of cancer therapy is 'last resort'
- Improvement in cardiac function
  - Beta-blocker and ACE inhibitors – small effect whole population
    - conflicting evidence on best class of agent
    - When to start??
    - For whom??
  - Can we prevent development of symptomatic heart failure with early intervention!?

19

Immunotherapy related myocarditis

20

Immunotherapy related myocarditis



Unleashes the immune system to attack cancer cells

21

Immunotherapy related myocarditis

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

22

Immunotherapy related myocarditis

Characteristic	Nivolumab (N=17,828)	Nivolumab plus Ipilimumab (N=1994)
	no. (%)	
Myocarditis		
Any*	10 (0.06)	8 (0.7)
Fatal events	1 (<0.01)	3 (0.2)
Myositis		
Any	27 (0.15)	7 (0.4)
Fatal events	2 (0.01)	1 (0.05)

* The number of patients with myocarditis includes six patients with concurrent myocarditis and myositis.

23

Immunotherapy related myocarditis

- Immunotherapy myocarditis – mechanism
  - Lymphocytic infiltration of myocardium and skeletal muscle
    - Other tissues spared – including smooth muscle
  - T-cell infiltrate T-cell receptors next-gen sequenced
    - High frequency clones in tumour and muscle infiltrate similar
    - ??similar epitopes being recognised
  - Appearance similar to acute rejection allograft after cardiac transplantation

24

Immunotherapy related myocarditis

- Myocarditis rare
  - Early onset
  - Fulminant progression
  - Incidence sub-clinical disease unknown
  - No clear evidence on patient selection or monitoring

25

Immunotherapy related myocarditis

CORRESPONDENCE

Alemtuzumab for Immune-Related Myocarditis Due to PD-1 Therapy

TO THE EDITOR:

June 13, 2019
N Engl J Med 2019; 380:2375-2376

26

Immunotherapy related myocarditis

- Case report
  - Alemtuzumab = anti-CD-52 (AKA Campath)
  - CD-52 - a protein present on the surface of
    - mature lymphocytes,
    - monocytes,
    - macrophages,
    - dendritic cells,
    - natural killer cells.
  - Alemtuzumab leads to complement-mediated destruction of these immune cells
  - In this patient, alemtuzumab led to rapid cytolytic induction of immunosuppression with the resolution of cardiac immune toxic effects.

27

Immunotherapy related myocarditis

Table 1. Biochemical Variables in Response to Different Methods of Immunosuppression.*

Biochemical Variable†	Day 1, Onset of Immune-Related Adverse Events	Day 7, Initial Response to Immuno-suppression	Day 18, Flare of Immune-Related Adverse Events before Alemtuzumab Treatment	Day 28, after Alemtuzumab Treatment	Day 50, after Weaning from Immuno-suppression
High-sensitivity troponin I — ng/ml	—	—	1.19	0.07	0.04
High-sensitivity troponin T — ng/liter	2373	797	1700	2002‡	488‡
Alanine aminotransferase — U/liter	238	38	180	37	34
Creatine kinase — U/liter	4300	190	650	236	63
C-reactive protein — mg/liter	—	—	45	4.7	3.2

28

Cardio-oncology

- Relatively new field
- Scope for interaction between two fascinating specialities
- Much research needed
  - Identify those at risk
  - Identify those affected
  - Manage cardiac risk and cancer in concert

29