Breast Cancer treatment related cardiotoxicity

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Overview

• Introduction to the problem
• Cardiac complications of radiotherapy
• Cardiac complications of chemotherapy
• Pre-treatment assessment and screening
• Monitoring during treatment imaging and biomarkers
• Prevention and management of cardiotoxicity
• Late effects
• Future directions
• Role of a Cardio-Oncology service
What’s the problem?

Estimated Number of Cancer Survivors in the US

Maddams 2012; DeSantis 2014
Cardiac problems with cancer treatment

Ghosh et al. British Journal of Hospital Medicine 2017
Radiotherapy-induced heart disease

- Cardiac effects can be divided into acute, consequential or late
- Acute damage is most common in rapidly proliferating cells damaged by radiation
- Consequential radiation damage is the chronic result of unhealed acute damage
- Late effects develop months to years later and are more common in tissues with a slow turnover
- Late manifestations common in cardiac tissue due to persistently elevated concentrations of inflammatory and proliferative markers in vascular endothelial cells
- Cardiac manifestations – pericarditis, myocardial fibrosis, CAD, valve lesions and arrhythmias
- RT-associated pericarditis can be very difficult to treat

Ghosh et al. Current Treatment Options in Cardiovascular Medicine 2018
Mechanisms of radiotherapy-induced heart disease

**Figure 1** Pathophysiological manifestations of radiation-induced heart disease for different radiosensitive structures within the heart. *LV*, Left ventricle; *RT*, radiotherapy.

Lancelloti et al JASE 2013
RIHD in breast cancer patients

- CV events due to accelerated endothelial injury and atherosclerosis can occur as early as 5y after left-sided thoracic RT and the risk persists for up to 30y
- Increased mean cardiac dose increased risk of HFpEF in a population-based case control study
- Acute and chronic pericarditis, valve regurgitation, sudden death described especially if dose >30Gy
- Autonomic dysfunction associated with increased all cause mortality
- Contemporary assessment of RIHD - Troponin and NT-pro BNP increased with RT for breast and lung cancer patients (Skytta 2015)
### Table 2 Risk factors of radiation-induced heart disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior or left chest irradiation location</td>
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<tr>
<td>High cumulative dose of radiation (&gt;30 Gy)</td>
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<tr>
<td>Younger patients (&lt;50 years)</td>
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<tr>
<td>High dose of radiation fractions (&gt;2 Gy/day)</td>
</tr>
<tr>
<td>Presence and extent of tumour in or next to the heart</td>
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<tr>
<td>Lack of shielding</td>
</tr>
<tr>
<td>Concomitant chemotherapy (the anthracyclines considerably increase the risk)</td>
</tr>
<tr>
<td>Cardiovascular risk factors (i.e. diabetes mellitus, smoking, overweight, ≥ moderate hypertension, hypercholesterolaemia)</td>
</tr>
<tr>
<td>Pre-existing cardiovascular disease</td>
</tr>
</tbody>
</table>

High-risk patients definition: anterior or left-side chest irradiation with ≥1 risk factors for RIHD.

Lancellotti et al. JASE 2013
Radiation dose considerations

- Every 1Gy increase in a study of 2168 patients increased CV event rate by 7.4% (Darby 2013)
- Darby suggested linear dose-side-effect relationship with no threshold
- Left sided RT – 1.19 to 1.9 increased risk of CVD mortality (Henson, Darby 2013)
- Newer techniques still result in cardiac perfusion defects (Zellars 2015)
Left versus right thoracic RT

- 199 Swedish breast cancer patients had RT and coronary angiography (Nilsson 2012)
- 4-7 x increase in significant LAD diagonal branch disease in those with left-sided tumours
- In right-sided tumours a non-significant higher incidence of proximal RCA lesions
- No difference for LMS or proximal LAD lesions (located posteriorly and usually out of tangential RT fields)
## Side effects of systemic breast cancer therapy

<table>
<thead>
<tr>
<th>Cancer Treatment</th>
<th>Cardiovascular Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines (eg, doxorubicin, epirubicin)</td>
<td>Left ventricular dysfunction, heart failure, myocarditis, pericarditis, atrial fibrillation, ventricular tachycardia, ventricular fibrillation</td>
</tr>
<tr>
<td>Alkylating agents (eg, cisplatin, cyclophosphamide)</td>
<td>Left ventricular dysfunction, heart failure, myocarditis, pericarditis, arterial thrombosis, bradycardia, atrial fibrillation, supraventricular tachycardia</td>
</tr>
<tr>
<td>Taxanes (eg, paclitaxel)</td>
<td>Bradycardia, heart block, ventricular ectopy</td>
</tr>
<tr>
<td>Antimetabolites (eg, 5-fluorouracil, capecitabine)</td>
<td>Coronary thrombosis, coronary artery spasm, atrial fibrillation, ventricular tachycardia, ventricular fibrillation</td>
</tr>
<tr>
<td>Endocrine therapy (eg, tamoxifen, anastrozole, letrozole)</td>
<td>Venous thrombosis, thromboembolism, peripheral atherosclerosis, dysrhythmia, valvular dysfunction, pericarditis, heart failure</td>
</tr>
<tr>
<td>HER-2–directed therapies (eg, trastuzumab, pertuzumab)</td>
<td>Left ventricular dysfunction, heart failure</td>
</tr>
<tr>
<td>Cyclin-dependent kinase 4/6 inhibitors (eg, palbociclib, ribociclib)</td>
<td>QTc prolongation</td>
</tr>
</tbody>
</table>
Mechanism of cytotoxicity and role of preventive therapies

Bloom Circ HF 2016
Anthracyclines

Types of toxicity
• Probably no safe dose threshold

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute Cardiotoxicity</th>
<th>Early-Onset Progressive Cardiotoxicity</th>
<th>Late-Onset Progressive Cardiotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Within the first week of anthracycline treatment</td>
<td>&lt;1 y after completion of anthracycline treatment</td>
<td>≥1 y after completion of anthracycline treatment</td>
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<tr>
<td>Risk factor dependence</td>
<td>Unknown</td>
<td>Yes*</td>
<td>Yes*</td>
</tr>
<tr>
<td>Clinical features in adults</td>
<td>Transient depression of myocardial contractility</td>
<td>Dilated cardiomyopathy</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Clinical features in children</td>
<td>Transient depression of myocardial contractility</td>
<td>Restrictive cardiomyopathy and/or dilated cardiomyopathy</td>
<td>Restrictive cardiomyopathy and/or dilated cardiomyopathy</td>
</tr>
<tr>
<td>Course</td>
<td>Usually reversible on discontinuation of anthracycline</td>
<td>Can be progressive</td>
<td>Can be progressive</td>
</tr>
</tbody>
</table>

Simbre Pead Drugs 2005
HER2 targeted therapy

- ErbB2 inhibition in cardiomyocytes may cause LVSD – may be reversible
- Adjuvant Trastuzumab decreased recurrence by 50% and mortality by 33% but in 5 trials – severe HF or cardiac event rate up to 4%
- HERA – greater effect in those treated for 2y Vs 1y
- No clear additional cardiotoxicity concerns yet with combined Trastuzumab and Pertuzumab use (APHINITY)
# Risk factors for cardiotoxicity

## At-risk therapies including any of the following:

- High-dose anthracycline therapy: doxorubicin $\geq 250$ mg/m\(^2\) or epirubicin $\geq 600$ mg/m\(^2\)
- High-dose radiation therapy when heart is in the field of treatment: radiotherapy $\geq 30$ Gy
- Sequential treatment: lower-dose anthracycline therapy (doxorubicin $< 250$ mg/m\(^2\) or epirubicin $< 600$ mg/m\(^2\)) and then subsequent treatment with trastuzumab
- Combination therapy: lower-dose anthracycline (doxorubicin $< 250$ mg/m\(^2\) or epirubicin $< 600$ mg/m\(^2\)) combined with lower-dose radiation therapy when heart is in the field of treatment ($< 30$ Gy)

## Presence of any of the following risk factors in addition to treatment with lower-dose anthracycline or trastuzumab alone:

- Older age at time of cancer treatment ($\geq 60$ y)
- $\geq 2$ CVD risk factors during or after cancer treatment: diabetes mellitus, dyslipidemia, hypertension, obesity, smoking
- History of myocardial infarction, moderate valvular disease, or low-normal left ventricular function (50%–55%) before or during cancer treatment

ASCO 2016
Screening, monitoring and management

Diagnostic Testing
- Echocardiography (including strain imaging)
- Cardiac magnetic resonance imaging
- MUGA scans
- Biochemical markers

Disease Progression
- Baseline CV Health & Risk Factors
  - Cancer Diagnosis
  - Pretreatment Surveillance
  - Cytotoxic Therapy
  - Cardiac Toxicity (LVEF decline, ACC/AHA Stage B)

Prevention and Treatment
- Primordial Prevention
- Primary Prevention
- Secondary Prevention
- Treatment
- • ACE Inhibitors or Angiotensin Receptor Blockers
  • Beta blockers
  • Statins
  • Exercise

CV Disease & Premature Death
Heart Failure (ACC/AHA Stage C &D)

AHA 2018
EF is not enough - components

Conceptually...

Ejection Fraction

Negishi 2010
Myocardial mechanics
EF is not enough - compensation

Negishi 2010
Strain in Cardio-Oncology

Changes in myocardial deformation occur earlier than changes in LVEF and at anthracycline doses lower than what was thought to be toxic (e.g. 200mg/m² of epirubicin).

2D-based strain (speckle-tracking) – decrease of 9-16% in peak systolic GLS during or immediately after anthracycline therapy (in absence of change in LVEF).

TDI-based strain – longitudinal SR (not strain) of basal septum decreases by 9-20% even at low dose epirubicin.

Strain <17% at 6 months after anthracyclines predictive of abnormal strain at 1 y F/U.

GLS an early predictor of LVSD with Trastuzumab.

Change in GLS more important than absolute numbers due to vendor variability in GLS values.

Figure 13 Initiation of a regimen potentially associated with type I toxicity. A baseline evaluation including measurements of LVEF, GLS, and troponin is recommended. If any are abnormal, a cardiology consultation is recommended. Follow-up is recommended at the completion of therapy and 6 months later for doses < 240 mg/m² or its equivalent. Once this dose is exceeded, measurements of LVEF, GLS, and troponin are recommended before each additional 50 mg/m².

Figure 14 Initiation of trastuzumab. A baseline evaluation including measurements of LVEF, GLS, and troponin is recommended. If any are abnormal, a cardiology consultation is recommended. Measurements of LVEF, GLS, and troponins are recommended every 3 months.
The role of biomarkers

Troponin

- Troponin rise within 3 d of high-dose chemotherapy predicts fall in LVEF
- Excellent negative predictive value for not developing cardiotoxicity during and immediately after treatment
- Troponin rises associated with irreversible Trastuzumab damage
- Rises can predict subsequent HF, pulmonary oedema and life-threatening arrhythmias
The role of biomarkers

NT-pro BNP, novel biomarkers and combined assessment

• Less consensus regarding role of NT-pro BNP in breast cancer cardiotoxicity diagnosis and prognosis
• Some studies have shown it predicts cardiotoxicity while others have not
• Compared to Troponin it may be more useful in detecting subclinical cardiotoxicity
• Early changes in HS-Trop and MPO predicted increased risk of 1\textsuperscript{st} cardiac event in breast CA patients treated with doxorubicin and trastuzumab
• Some growth factors may be predictive – more work required
• GLS and Troponin 3 m after doxorubicin predicted cardiotoxicity at 6 m
• 10\% change in GLS and increased Troponin predicted cardiotoxicity with a specificity of 97\% and a NPV of 97\%
Cardioprotection - dexrazoxanone

- Dexrazoxanone used as a chelator binds to intracellular iron decreasing free radical production
- Changes conformation of TOP2B and interferes with anthracycline binding
- Meta-analysis of 7 trials (1000 patients) estimated an overall reduction of 65% in cardiac events (Vs placebo)
- A Cochrane review has shown that it does not decrease treatment efficacy or cancer response rates
- No clear increased risk of second malignancy but this controversy has narrowed FDA licence to metastatic breast CA patients with a cumulative doxorubicin dose of $\geq 300\text{mg/m}^2$. EMA also includes those with a minimum dose of 540mg/m2 of epirubicin.
Cardioprotection – anthracyclines and RT

- Cumulative dose restrictions but probably no safe dose
- Liposomal anthracyclines to promote greater accumulation in the tumour – associated with lower cardiotoxicity in 1 study
- Anthracycline analogues – epirubicin and idarubicin – have not shown significant cardioprotective benefits
- Mitoxantrone – no clear cardiac benefit
- Continuous ivi – appears less cardiotoxic in the acute setting but unclear if any long-term benefit
- Newer RT techniques – proton therapy, deep-inspiration breath-holding, respiratory gating, lateral decubitus positioning, 3D planning – long-term efficacy unknown
Can we prevent it - PRADA

<table>
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<tr>
<th></th>
<th>n</th>
<th>Baseline</th>
<th>EOS</th>
<th>Change from baseline to EOS</th>
<th>Between-group difference in change from baseline to EOS</th>
<th>P-value</th>
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<td>No candesartan</td>
<td>60</td>
<td>63.2 (62.0, 64.4)</td>
<td>60.6 (59.4, 61.8)</td>
<td>−2.6 (−3.8, −1.5)</td>
<td>1.9 (0.2, 3.5)</td>
<td><strong>0.026</strong></td>
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<td>−0.8 (−1.9, 0.4)</td>
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<td>62.8 (61.6, 64.0)</td>
<td>61.0 (59.8, 62.2)</td>
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<td>0.2 (−1.4, 1.9)</td>
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<tr>
<td>Metoprolol</td>
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<td>62.5 (61.3, 63.7)</td>
<td>61.0 (59.8, 62.2)</td>
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<td>0.2 (−1.4, 1.9)</td>
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<td><strong>RVEF</strong></td>
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<td>61.3 (60.0, 62.5)</td>
<td>58.9 (57.6, 60.1)</td>
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<tr>
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<td>60.4 (59.2, 61.6)</td>
<td>58.0 (56.8, 59.3)</td>
<td>−2.4 (−3.7, −1.1)</td>
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<td>61.1 (59.8, 62.3)</td>
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<td>−1.6 (−2.9, −0.3)</td>
<td>0.8 (−1.0, 2.6)</td>
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<td><strong>LV GLS</strong></td>
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<td>−0.7 (−1.4, 0.1)</td>
<td>0.076</td>
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<td>No metoprolol</td>
<td>46</td>
<td>−21.4 (−21.9, −20.8)</td>
<td>−21.0 (−21.6, −20.5)</td>
<td>0.3 (−0.2, 0.8)</td>
<td>−0.1 (−0.8, 0.7)</td>
<td>0.824</td>
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<tr>
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<td>47</td>
<td>−21.5 (−22.0, −21.0)</td>
<td>−21.3 (−21.8, −20.7)</td>
<td>0.2 (−0.3, 0.7)</td>
<td>−0.1 (−0.8, 0.7)</td>
<td>0.824</td>
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<tr>
<td>No candesartan</td>
<td>63</td>
<td>7.1 (6.6, 7.6)</td>
<td>7.2 (6.7, 7.7)</td>
<td>0.1 (−0.4, 0.5)</td>
<td>0.1 (−0.5, 0.8)</td>
<td><strong>0.009</strong></td>
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<tr>
<td>Candesartan</td>
<td>59</td>
<td>7.4 (6.9, 7.9)</td>
<td>7.6 (7.1, 8.1)</td>
<td>0.2 (−0.2, 0.7)</td>
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<td>0.688</td>
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<td>0.8 (0.2, 1.5)</td>
<td>0.688</td>
</tr>
</tbody>
</table>

Gulati EHJ 2016
The earlier the better

- Decreased time to treatment with enalapril +/- carvedilol independent predictor of LVEF recovery
- Combination therapy may be more effective
- 1 study showed attenuated decline in LVEF and diastolic stabilization when spironolactone was used with anthracyclines in breast CA patients (Akpek 2015)

Cardinale JACC 2010
Timing of cardiac function assessment including post-therapy

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>During Therapy</th>
<th>Post-Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline Therapy</td>
<td>Yes</td>
<td>If cumulative dose &gt;240 mg/m² then imaging prior to each additional dose of 50 mg/m²</td>
<td>At completion of therapy &amp; 6 months later in those with cumulative dose &lt;240 mg/m²</td>
</tr>
<tr>
<td>HER2 Targeted Therapy</td>
<td>Yes</td>
<td>Every 3 months during treatment</td>
<td>No routine testing if asymptomatic</td>
</tr>
<tr>
<td>HER2 Targeted Therapy after Prior Treatment with Anthracycline</td>
<td>Yes</td>
<td>Every 3 months during treatment</td>
<td>6 months later</td>
</tr>
</tbody>
</table>

ASE/EACVI 2014
What about late effects?

• ASE/EACVI - After completion of anthracycline therapy should have yearly assessment by a "healthcare provider". Repeat cardiac imaging discretionary based on history and physical examination.

• Consensus document (Circ HF 2016) mentions imaging up till 18 months in medium to high risk patients.
ASCO late effects guidance

5. What are the preferred surveillance and monitoring approaches after treatment in patients at risk for cardiac dysfunction?

Recommendation 5.1. Clinicians should complete a careful history and physical examination in survivors of cancer previously treated with potentially cardiotoxic therapies.

(Evidence based; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 5.1.1. In individuals with clinical signs or symptoms concerning for cardiac dysfunction, the following approaches should be offered as part of recommended care:

- Echocardiogram for diagnostic workup
  (Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)
- Cardiac MRI or MUGA if echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI
  (Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)
- Serum cardiac biomarkers (troponins, natriuretic peptides)
  (Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)
- Referral to a cardiologist based on findings
  (Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 5.2. An echocardiogram may be performed between 6 and 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of cardiac dysfunction.

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 5.2.1. Cardiac MRI or MUGA may be offered for surveillance in asymptomatic individuals if an echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI.

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 5.3. Patients identified to have asymptomatic cardiac dysfunction during routine surveillance should be referred to a cardiologist or a health care provider with cardio-oncology expertise for further assessment and management.

(Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 5.4. No recommendations can be made regarding the frequency and duration of surveillance in patients at increased risk (Recommendation 1.1) who are asymptomatic and have no evidence of cardiac dysfunction on their 6- to 12-month post-treatment echocardiogram.

(Informal consensus; relative balance of benefits and harms; Evidence quality: insufficient)

Recommendation 5.5. Clinicians should regularly evaluate and manage cardiovascular risk factors such as smoking, hypertension, diabetes, dyslipidemia, and obesity in patients previously treated with cardiotoxic cancer therapies. A heart-healthy lifestyle, including the role of diet and exercise, should be discussed as part of long-term follow-up care.

(Evidence based and consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)
For the future

• More effective predictors of cardiotoxicity and components of optimal screening
• Cardiotoxicity of newer systemic agents
• Effects of CVD RF modification on M+M in cancer patients
• Better understanding of combined chemotherapy and radiotherapy adverse effects
• Standardized definition of cardiotoxicity with international collaboration
• Increased Cardio-Oncology collaborative working
What is the role of a Cardio-Oncology service in the care of breast cancer patients?

- Work with breast oncologists to determine best practice for CV screening
- Try to determine cost-effective practice
- Develop local guidelines to this effect
- Detect abnormalities early and intervene appropriately
- Determine local late effects follow up
- Educational activities – departmental, fellows, courses
- Participate in local/national/international research in collaboration

Ghosh et al. Indian Heart Journal 2017
What is the role of a Cardio-Oncology service in the care of breast cancer patients?

Ghosh et al. Indian Heart Journal 2017

Ghosh et al. British Journal of Cardiology 2017
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