Breast Cancer in Older Adults
Cardiac Toxicity in Breast Cancer

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Specialist Pharmacist (Oncology)
Learning Objectives

♥ At the end of this short presentation, one should be able to

♥ List the common chemotherapy &/or targeted therapies that can cause cardiotoxicity

♥ Distinguish cardiotoxicity arising from conventional chemotherapy & targeted agents

♥ Discuss the appropriate preventive, monitoring & treatment of cardiotoxicity caused by drugs used in cancer therapy
Overview

♥ Introduction – drugs involved & definition
♥ Mechanism of cardiotoxicity
♥ Risk Factors
♥ Monitoring of cardiotoxicity
♥ Review of trastuzumab-induced cardiotoxicity in elderly
♥ Treatment of chemotherapy-induced cardiotoxicity
Case

Mrs JBI, a 65 yr old lady newly diagnosed with (L) Stage IIA breast cancer (ER/PR –ve, HER2 +ve)

s/p SMAC on 15th Jan 2014

Treatment Plan

IV AC (doxorubicin 60mg/m² & cyclophosphamide 600mg/m²) chemo every 3 wkly x 4 cycles
→ followed by wkly Paclitaxel / Trastuzumab (TH) x 12
→ then maintenance trastuzumab every 3 wkly (total 1 yr)
Case (cont’d)

♥ PMHx: HTN (x 5yr)
♥ ALL: Allergic to CT contrast → rashes
♥ Drug: Amlodipine 10mg OM

♥ Social History
  – Non-smoker, non-alcoholic drinker

♥ ECOG: 0
♥ Height = 152cm, Weight: 75.7kg
♥ BSA = 1.8m², BMI 32kg/m²
♥ Baseline LVEF (MUGA) = 65%
Cardiovascular Side Effects of Modern Cancer Therapy

- Arrhythmias
- Hypertension
- Thrombosis
- Myocardial Ischemia
- Impaired myocardial contraction (systolic / diastolic dysfunction)
# Cardiotoxicity of Antineoplastics

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antitumour antibiotics</td>
<td>Eg Anthracycline</td>
<td>Cardiomyopathy, arrhythmias, CHF, Cumulative dose</td>
</tr>
<tr>
<td>Microtubule targeting agents</td>
<td>Eg Taxanes</td>
<td>Bradycardia, arrhythmias, CHF, MI, Typically reversible, may potentiate anthracycline toxicity</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Eg Cisplatin, Cyclophosphamide</td>
<td>Arrhythmias, heart block, CHF, Coronary vasospasm, Electrolyte abnormalities, endothelial capillary damage</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Eg Fluorouracil</td>
<td>Cardiac failure, MI, Likely Mechanism: Coronary vasospasm</td>
</tr>
</tbody>
</table>

Floyd JD et al. JCO 2005;23:7685-7696
# Cardiotoxicity Associated with Targeted Therapies

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Incidence (%)</th>
<th>Clinical Characteristics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal Antibodies</strong></td>
<td></td>
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</tr>
<tr>
<td>Trastuzumab</td>
<td>2 – 28</td>
<td>Potentially reversible, significant decline in LVEF</td>
<td><strong>Clinical:</strong> Age, preexisting cardiac disease, borderline LVEF before therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Treatment related:</strong> prior anthracycline exposure, sequence of chemotherapy exposure</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1.7 – 3</td>
<td>Not completely defined, systolic dysfunction</td>
<td>Previous anthracycline use</td>
</tr>
<tr>
<td><strong>Tyrosine Kinase Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>1.5 – 2.2</td>
<td>Not completely defined, systolic dysfunction</td>
<td>Not completely defined, perhaps prior anthracycline use</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>2.7 -11</td>
<td>Possibly reversible, significant decline in LVEF, HF</td>
<td>History of coronary disease</td>
</tr>
<tr>
<td>Imatinib</td>
<td>0.5 – 1.7</td>
<td>Not completely defined, systolic dysfunction</td>
<td>Not completely defined</td>
</tr>
</tbody>
</table>

Wells QS, Lenihan DJ. Prog Cardiovasc Dis 2010;53:140-8
Definition of Cardiotoxicity
# Definition of Cardiotoxicity

<table>
<thead>
<tr>
<th>National Cancer Institute</th>
<th>Cardiac Review &amp; Evaluation Committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>♥ Toxicity that affects the heart</td>
<td>♥ Cardiomyopathy in terms of ↓ LVEF, either global or more severe in the septum</td>
</tr>
<tr>
<td></td>
<td>♥ Symptomatic HF</td>
</tr>
<tr>
<td></td>
<td>♥ Signs associated with HF, such as S3 gallop, tachycardia or both</td>
</tr>
<tr>
<td></td>
<td>♥ Reduction in LVEF</td>
</tr>
<tr>
<td></td>
<td>- &lt; 5% to &lt; 55% <strong>WITH</strong> OR</td>
</tr>
<tr>
<td></td>
<td>- ≥ 10% to &lt; 55% <strong>WITHOUT</strong> S/Sx of HF</td>
</tr>
</tbody>
</table>
Anthracycline vs Trastuzumab

(1) How does Cardiotoxicity arise?
**Anthracycline-induced Cardiotoxicity (AIC)**

- Top 2B alters the tension of DNA during replication & transcription by breaking, twisting, and resealing DNA

- Anthracyclines intercalate into DNA → forms complex with Top2B → inhibits Top2B enzymatic activity

- DNA double strand breaks
Anthracycline-induced Cardiotoxicity (AIC)

**Injury (days to wk after therapy)**
- Troponin I released at time of exposure
- Cell death

**Heart compensates & remodelling occurs**
- Either short phase or indefinitely
- EF may remain substantially normal

**Heart NO longer compensates**
- Symptomatic HF ensues

Stage 1

Stage 4
Trastuzumab induced Cardiotoxicity (TIC)

- Cardiac endothelial cells → Neuregulin 1 (NRG1)
- Binds to human epidermal growth factor receptor 4 → Promotes heterodimerization with HER2
- Activation of downstream intracellular signalling pathways
## Type I vs Type II Cardiotoxicity

<table>
<thead>
<tr>
<th></th>
<th>Type I Cardiotoxicity (eg anthracycline)</th>
<th>Type II Cardiotoxicity (eg Trastuzumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical course, response to medication</strong></td>
<td>May stabilise, but subclinical damage seems to persist; recurrence in mths or yrs may be related to sequential cardiac stress</td>
<td><strong>High likelihood</strong> of complete or near-to-complete recovery upon withdrawal &amp;/or medication</td>
</tr>
<tr>
<td><strong>Dose dependence</strong></td>
<td><strong>Cumulative</strong>: “lifetime” dose-related</td>
<td>Dose-independent</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Free radical formation (?), alcohol metabolite formation (?)</td>
<td>Elimination of HER2-related survival factors</td>
</tr>
<tr>
<td><strong>Ultrastructure</strong></td>
<td>Vacuoles, myofibrillar disarray &amp; dropout, apoptosis &amp; necrosis</td>
<td>With limited exceptions, no apparent ultrastructural abnormalities</td>
</tr>
<tr>
<td><strong>Non-invasive testing</strong></td>
<td>↓ LVEF , global ↓ in wall motion</td>
<td></td>
</tr>
<tr>
<td><strong>Effect of rechallenge</strong></td>
<td><strong>High probability of recurrent dysfunction</strong> that progresses toward treatment-resistant CHF</td>
<td>↑ evidence for safety of rechallenge</td>
</tr>
<tr>
<td><strong>Effect of late sequential stress</strong></td>
<td>High likelihood of sequential stress-related cardiac dysfunction</td>
<td>Low likelihood of sequential stress-related cardiac dysfunction</td>
</tr>
</tbody>
</table>

Anthracycline vs Trastuzumab

(2) Risk factors
Risk Factors (AIC)

♥ Therapy-related
  ♥ Type & formulation of anthracyclines

♥ Cumulative dose

♥ Infusion time
  (eg IVP or CI)

♥ Combination
  &/or sequence of chemotherapy

♥ Prior or concomitant mediastinal RT

Risk Factors (AIC)

♥ Patient-related

♥ Age

♥ Gender (eg females)

♥ Cardiovascular disease (CVD)

♥ Presence of cardiovascular (CV) risk factors

Risk Factors (TIC)

♥ Age > 60 yr
♥ Low baseline LVEF
♥ Prior anthracycline exposure
♥ Current or previous treatment with anti-hypertensive medication
♥ Higher body mass index (> 25kg/m²)
♥ Alcohol intake
♥ HER2 polymorphisms

Case

Mrs JBI has completed AC chemo x 4 cycles & about to begin wkly paclitaxel / trastuzumab treatment

How should patient be monitored for cardiac function?

Is it necessary since patient has already completed anthracycline treatment?
ESMO Clinical Practice Guidelines: Recommendations for Cardiotoxicity Monitoring

♥ Periodic monitoring of cardiac function with Decho is suggested especially for anthracyclines & their derivates or monoclonal Ab

♥ Periodic monitoring (every 12 wks) of cardiac function is also suggested for patients receiving monoclonal Ab, esp if prev treated with anthracycline

♥ LVEF reduction of ≥ 20% from baseline despite normal function OR LVEF decline < 50% necessitate reassessment or discontinuation of therapy & further frequent clinical & echographic checks

Limitations / Imperfections of LVEF

♥ Subjectivity

♥ ↓ LVEF often deemed as being related to offending agent

♥ Unchanged LVEF = Lack of cardiotoxicity?

♥ ↓ LVEF after treatment may be a marker for advanced myocyte damage

Case

Mrs JBI has completed AC x 4 cycles & had a MUGA scan prior to trastuzumab, LVEF = 55% (pre-chemo LVEF = 65%)

She went on to receive TH x 12 doses

Routine MUGA scan performed post TH reported a LVEF = 48%, no RWMA. She is asymptomatic & well otherwise

Would you proceed with maintenance trastuzumab therapy?
Schema for adjuvant trastuzumab trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median age; % “elderly”</th>
<th>NSABP B-31 &amp; N 9831</th>
<th>HERA: 49; ≥ 60yrs 16.2%</th>
<th>BCIRG 06: ~ 48% older than 50 yrs</th>
<th>FinHER: 50 – 51yrs; NR (recruited pts &lt; 66 yr)</th>
<th>PACS 04: (recruited pts &lt; 65 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31</td>
<td></td>
<td>NR</td>
<td>&gt; 60yrs 16.2%</td>
<td></td>
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</tr>
<tr>
<td>AC → PTX</td>
<td></td>
<td>11.7%</td>
<td>0%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AC → PTX + HER</td>
<td></td>
<td>0.5%</td>
<td>0%</td>
<td></td>
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<tr>
<td>NCCTG N9831</td>
<td></td>
<td>5%</td>
<td>0.6%</td>
<td></td>
<td></td>
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<tr>
<td>AC → PTX</td>
<td></td>
<td>6.6%</td>
<td>3.3%</td>
<td></td>
<td></td>
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<tr>
<td>AC → PTX + HER</td>
<td></td>
<td>0.5%</td>
<td>0%</td>
<td></td>
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<tr>
<td>HERA</td>
<td></td>
<td>3%</td>
<td>NR</td>
<td></td>
<td></td>
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<tr>
<td>CTx (+/−) RT</td>
<td></td>
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<tr>
<td>CTx (+/−) RT → HER (1y)</td>
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<tr>
<td>CTx (+/−) RT → HER (2y)</td>
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<tr>
<td>BCIRG 06</td>
<td></td>
<td>NR</td>
<td>0.7%</td>
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<tr>
<td>AC → DTX</td>
<td></td>
<td>NR</td>
<td>2%</td>
<td></td>
<td></td>
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<tr>
<td>AC → DTX + HER</td>
<td></td>
<td>NR</td>
<td>0.4%</td>
<td></td>
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<tr>
<td>TCH + HER</td>
<td></td>
<td>10.5%</td>
<td>1.7%</td>
<td></td>
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</tr>
<tr>
<td>FinHER</td>
<td></td>
<td>6.8%</td>
<td>0.9%</td>
<td></td>
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</tr>
<tr>
<td>DTX or VNR → FEC</td>
<td></td>
<td>4.2%</td>
<td>0.4%</td>
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<tr>
<td>DTX or VNR + HER → FEC</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PACS 04</td>
<td></td>
<td>14.2%</td>
<td>1.5%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FEC or ED</td>
<td></td>
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<tr>
<td>FEC or ED → HER (1y)</td>
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Systolic dysfunction Severe CHF

- NSABP B-31 & N 9831
- HERA: 49; ≥ 60yrs 16.2%
- BCIRG 06: ~ 48% older than 50 yrs
- FinHER: 50 – 51yrs; NR (recruited pts < 66 yr)
- PACS 04: (recruited pts < 65 yrs)
NCCS Own Retrospective Data TIC (adjuvant) from 2005 to 2011

♥ N = 314
♥ Median age = 52 (25 to 77 yrs)
♥ Mean baseline LVEF = 61.1% ± 6 (50 – 79%)

♥ Incidence of TIC = 39.5% (≥ 60 yrs = 17.7%)
♥ Asymptomatic decline in LVEF = 77.4%
♥ Mean time for onset of TIC was 4.7 ± 2.7 mths (0.5 to 14)
♥ 32.6% had recurrence TIC upon rechallenge

♥ Factors that predicted for TIC included (p < 0.05)
  ♥ Low normal pre-trastuzumab LVEF (<60%)
  ♥ Prior anthracycline
  ♥ Decline in LVEF pre-anthracycline & before trastuzumab
  ♥ BMI > 23kg/m²
# TIC in Elderly Breast Cancer Patients

<table>
<thead>
<tr>
<th>Ref</th>
<th>Patient population / Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarantini L et al</td>
<td>Early stage breast cancer Multicenter Italian Jan 2008 to Jun 2009 Adjuvant trastuzumab + chemo</td>
<td>N= 499 [68% (≤ 60 yrs), 32% pts (&gt; 60yrs) ]</td>
</tr>
</tbody>
</table>
| Ann Oncol 2012;23:305 8-63 |                                                                                               | **Multivariate logistic regression**  
Independent predictors of TIC  
Age > 60 yrs  
(HR 1.76; 95% CI 1.15 – 2.7, p=0.009) &  
Prior adjuvant therapy with doxorubicin  
(HR 2.14; 95% CI 1.2 -3.83, p=0.01) |
### TIC in Elderly Breast Cancer Patients

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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serrano C et al</td>
<td>HER2 +ve early or advanced BC pts Retrospective (from 2005) At least 1 dose of trastuzumab &amp; 2 LVEF measurements</td>
<td>N= 45 pts, median age = 75.9 yrs (70 -92)</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab based chemo regimens</td>
<td><strong>ASYMPTOMATIC cardiotoxicity</strong> (↓ ≥ 10% to LVEF &lt;50% OR LVEF ↓ of 20%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Total % of pts: 17.8%</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>SYMPTOMATIC CHF</strong> 8.9% - all with advanced breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median time of recovery = 5 wks (3-21) (All except one)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Patients with TIC presented more often with cardiovascular risk factors, such as</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1)Cardiac disease (33% vs 9.1%, p=0.017) &amp; (2)DM (33.3% vs 6.1%, p=0.01)</td>
</tr>
</tbody>
</table>
## TIC in Elderly Breast Cancer Patients

<table>
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<tr>
<th>Ref</th>
<th>Patient population / Treatment</th>
<th>Results</th>
</tr>
</thead>
</table>
| Chavez-MacGregor M et al     | Used SEER-Medicare & Texas Cancer Registry-Medicare linked database At least 66 yr old Stage I to III BC 2005 to 2009 Chemo +/- Trastuzumab                                                                                                               | N= 9,535 (23.1% received trastuzumab) Median age = 71 yr **Trastuzumab users vs non-trastuzumab users** Rate of CHF:29.4% vs 18.9% (p<0.001)  
**Trastuzumab users were more likely to develop CHF** than non-trastuzumab users **Increased risk of CHF (trastuzumab users)**  
Older age > 80 yrs (HR 1.53; 95% CI, 1.16 to 2.10)  
CAD (HR 1.82; 95% CI, 1.34 to 2.48)  
HTN (HR 1.24; 95% CI, 1.02 to 1.50)  
Wkly Trastuzumab admin (HR 1.33; 95% CI, 1.05 to 1.68) |
| Adamo V et al                | HER2+ve BC patients ≥ 70 yrs 2005 to 2010 Trastuzumab based regimen                                                                                                                                                               | Evaluable pts = 51, Median age = 76 yrs (70 – 86) **TIC reported in 7 pts (13.7%)**  
1 (CHF), 3 (LVEF decline by >15% to < 50%) & other 3 (LVEF decline of >10% but above 50%) |
Case (cont’d)

2 years later, Mrs JBI was diagnosed with metastatic breast cancer → liver (ER/PR –ve, HER2 +ve)

Plan was to initiate
- IV Pertuzumab 840mg (C1) then 420mg (C2 onwards)
- IV Trastuzumab 8mg/kg (C1) then 6mg/kg (C2 onwards)
- IV Docetaxel 75mg/m²
  All administered on D1 every 3 wkly

In view of previous decline in LVEF with trastuzumab therapy, would there be a concern of increased risk for cardiotoxicity with dual anti-HER2 therapy?
# Cardiac toxicity with DUAL HER2 blockade

<table>
<thead>
<tr>
<th>Anti-HER2 Therapy</th>
<th>MONOtherapy (n=1,473)</th>
<th>DUAL therapy (n=1,142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>1.49% (95% CI: 0.98 – 2.23%)</td>
<td>0.88% (95% CI: 0.47 – 1.64%)</td>
</tr>
<tr>
<td>LVEF decline</td>
<td>2.9% (95% CI: 2.1 – 4.1%)</td>
<td>3.1% (95% CI: 2.2 – 4.4%)</td>
</tr>
</tbody>
</table>

♥ Pooled OR for CHF in patients receiving dual anti-HER2 vs anti-HER2 monotherapy = 0.58 (95% CI: 0.26 – 1.27; p value = 0.17)

♥ Pooled OR for LVEF decline with dual anti-HER2 tx vs anti-HER2 monotherapy = 0.88 (95% CI: 0.53 – 1.48; p value = 0.64)

Treatment of Chemotherapy-induced Cardiotoxicity
Treatment of anthracyline-induced cardiotoxicity

♥ Prospective, single centre study (N = 201)

♥ Patients with LVEF ≤ 45% & absence of any identifiable cause of CMP

♥ Primary end point: LVEF response to HF therapy

♥ Treatment: Enalapril &/or carvedilol

Figure 1: Percentage of Responders According to the Time Elapsed From AC Administration and Start of HF Therapy

Responders: LVEF ↑ up to 50%
Partial responders: LVEF ↑ at least 10% but < 50%
Non-responders: LVEF ↑ < 10% & not reach 50%
Change in LVEF from baseline to rechallenge with trastuzumab

Cardiac Risk Assessment

Cardiac Imaging

Clinical risk factors

Biomarkers

Eg Speckle-tracking imaging
Cardiac MRI

Personalised cardiac risk assessment

Risk prediction model

Cost effective screening & prevention

Eg troponins, natriuretic peptides

MANTICORE trial
Use of conventional HF medications to prevent TIC

Take home message…

♥ Cardiotoxicity is one of the most important complications arising from cancer treatment

♥ Crucial to have reliable biomarkers to identify high risk patients & initiate prompt treatment when necessary

♥ Clinical endpoints of cardiotoxicity & cardiac monitoring need to be standardised

♥ Multidisciplinary team approach is required
Thank you

Email: npaslc@nccs.com.sg
Effect of Various Modifying Factors on Risk of Cardiotoxicity

**MODIFIABLE Cardiotoxicity Risk Factors**
- Limitation of cumulative dose
- Continuous vs bolus infusion
- Cardioprotectants (Dexrazoxane-Liposomal anthracyclines)
- Rate of administration
- Cumulative dose (mg/m\(^2\))
  - Doxorubicin: 450
  - Daunorubicin: 550
  - Epirubicin: 900
- Concomitant RT & other chemotherapy agents

**NON-MODIFIABLE Cardiotoxicity Risk Factors**
- Gender
- Age
- Genetic Factors