Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy and its management, considering also cachexia

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Member ESMO supportive care Faculty
Board member and Past-President of MASCC
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And Honorary President of AFSOS
(French-speaking Association for Supportive Care)
Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines†

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review

Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper

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Breast Cancer in Older Adults
Cardiac Toxicity in Breast Cancer

Dr Vivianne Shih, Pharm.D., BCPS, BCOP
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
Cardiovascular Side Effects of Modern Cancer Therapy

- Arrhythmias
- Hypertension
- Thrombosis
- Myocardial Ischemia
- Impaired myocardial contraction (systolic / diastolic dysfunction)

Cardiotoxicity
## Cardiotoxicity of Antineoplastics

<table>
<thead>
<tr>
<th>Category</th>
<th>Effects</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antitumour antibiotics</td>
<td>Cardiomyopathy, arrhythmias, CHF</td>
<td>Bradycardia, arrhythmias, CHF, MI</td>
</tr>
<tr>
<td>Eg Anthracycline</td>
<td>• Cumulative dose</td>
<td>• Typically reversible, may potentiate anthracycline toxicity</td>
</tr>
<tr>
<td>Microtubule targeting agents</td>
<td>Bradycardia, arrhythmias, CHF, MI</td>
<td>Arrhythmias, heart block, CHF</td>
</tr>
<tr>
<td>Eg Taxanes</td>
<td>• Typically reversible, may potentiate anthracycline toxicity</td>
<td>• Mechanism: Electrolyte abnormalities; endothelial capillary damage</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Arrhythmias, heart block, CHF</td>
<td>Cardiac failure, MI</td>
</tr>
<tr>
<td>Eg Cisplatin, Cyclophosphamide</td>
<td>• Mechanism: Electrolyte abnormalities; endothelial capillary damage</td>
<td>• Likely Mechanism: Coronary vasospasm</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Cardiac failure, MI</td>
<td></td>
</tr>
<tr>
<td>Eg Fluorouracil</td>
<td>• Likely Mechanism: Coronary vasospasm</td>
<td></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>
<td></td>
<td></td>
</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>‒ ≤ 5% to &lt; 55% WITH OR</td>
</tr>
<tr>
<td></td>
<td>‒ &gt; 10% to &lt; 55% WITHOUT 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 & 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**
  - $\rightarrow$ Neuregulin 1 (NRG1)

- **Binds to human epidermal growth factor receptor 4**
  - $\rightarrow$ 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>Clinical course,</td>
<td>May stabilise, but subclinical <strong>damage</strong> seems to <strong>persist</strong>; recurrence in mths or yrs may be related to</td>
<td><strong>High likelihood</strong> of <strong>complete or near-to-complete recovery</strong> upon withdrawal &amp;/or medication</td>
</tr>
<tr>
<td>response to medication</td>
<td>sequential cardiac stress</td>
<td></td>
</tr>
<tr>
<td>Dose dependence</td>
<td><strong>Cumulative; “lifetime” dose-related</strong></td>
<td><strong>Dose-independent</strong></td>
</tr>
<tr>
<td>Mechanism</td>
<td>Free radical formation (?), alcohol metabolite formation (?)</td>
<td>Elimination of HER2-related survival factors</td>
</tr>
<tr>
<td>Ultrastructure</td>
<td>Vacuoles, myofibrillar disarray &amp; dropout, apoptosis &amp; necrosis</td>
<td>With limited exceptions, no apparent ultrastructural abnormalities</td>
</tr>
<tr>
<td>Non-invasive testing</td>
<td>↓ LVEF, global ↓ in wall motion</td>
<td></td>
</tr>
<tr>
<td>Effect of rechallenge</td>
<td><strong>High probability of recurrent</strong> dysfunction that progresses toward treatment-resistant CHF</td>
<td>↑ evidence for <strong>safety of rechallenge</strong></td>
</tr>
<tr>
<td>Effect of late sequential stress</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

Risk factors for radiation-associated heart damage include:

- dose >30–35 Gy
- dose per fraction >2 Gy
- large volume of irradiated heart
- younger age at exposure
- longer time since exposure
- use of cytotoxic chemotherapy
- endocrine therapy or trastuzumab
- presence of other risk factors such as diabetes, hypertension, dyslipidaemias, obesity, smoking etc.
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 $\geq 20\%$ 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

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

<table>
<thead>
<tr>
<th>Responders (%)</th>
<th>1-2</th>
<th>2-4</th>
<th>4-8</th>
<th>6-8</th>
<th>9-10</th>
<th>10-12</th>
<th>&gt;12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=75)</td>
<td>64%</td>
<td>28%</td>
<td>7%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**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%

Cardinale D et al. JACC 2010;55:213-20
Change in LVEF from baseline to rechallenge with trastuzumab

Cardiac Risk Assessment

Cardiac Imaging

Eg Speckle-tracking imaging
Cardiac MRI

Clinical risk factors

Personalised cardiac risk assessment

Biomarkers

Eg troponins, natriuretic peptides

Risk prediction model

Cost effective screening & prevention

MANTICORE trial
Use of conventional HF medications to prevent TIC

Effect of Various Modifying Factors on Risk of Cardiotoxicity

**PREVENTION**

- Limitation of cumulative dose
- Continuous vs bolus infusion
- Cardioprotectants (Dexrazoxane-Liposomal anthracyclines)
- Concomitant RT & other chemotherapy agents

**MODIFIABLE Cardiotoxicity Risk Factors**

- Rate of administration
- Cumulative dose (mg/m²)
  - Doxorubicin: 450
  - Daunorubicin: 550
  - Epirubicin: 900

**NON-MODIFIABLE Cardiotoxicity Risk Factors**

- Gender
- Age
- Genetic Factors

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
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SUPPORTIVE CARE IN CANCER
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AND REMEMBER AFSOS AND TAO
IN PARIS IN THE FALL