Risk of cardiovascular toxicity in cancer patients

Ghada Sayed Youssef
Lecturer of cardiology, Cairo University

Cardiotoxicity: Why?

- Direct effects of cancer treatment on heart structure and function
  - Radiation induced toxicity
  - Chemotherapy induced toxicity
  - Hormonal induced toxicity
  - Interaction of therapies

- Accelerated development of CVD, especially if with risk factors
Cardiotoxicity: How?

**Anthracyclines**
- Iron-dependent oxygen free radicals
- Peroxidation of lipids in the membranes of myocardial mitochondria
- Suppression of DNA, RNA and proteins synthesis as well as of important transcription factors
- Altering adrenergic and adenylyl cyclase activity
- Disrupt calcium homeostasis


Myocardial necrosis, apoptosis and fibrosis

Cardiotoxicity: How?

**Trastuzumab**
- Modifies mitochondrial integrity via the BCL-X (B-cell CLL/lymphoma-X) protein family
- Depleting ATP
- Leading to contractile dysfunction

Rochette et al. Trends in pharmacological sciences, 2015
Cardiotoxicity: How?

Radiotherapy
- Lymphomas, lung or breast cancers
- Substantial part of the heart should be involved
- Mechanism: endothelial cell affection, vascular damage and accelerated atherosclerosis

Hormonal-therapy related cardiotoxicity
- Breast cancer pts
- Years after cancer
- Venous thromboembolism
- Vascular events: MI and angina
Tamoxifen and venous thromboembolism

Aromatase inhibitors and vascular events
Cardiotoxicity: What?

- Myocardial dysfunction and heart failure (HF)
- Coronary artery disease (CAD)
- Valvular disease
- Pericardial complications
- Arrhythmias, especially those induced by QT-prolonging drugs
- Arterial hypertension
- Pulmonary hypertension
- Peripheral vascular disease and stroke
- Thromboembolic disease

Gziri et al. Prenatal diagnosis, 2012
Cardiotoxicity: When?

- Early
- Late
- Transient
- Permanent

Prevention of cardiotoxicity
Mitigate CV risks

Predict before initiation of therapy

- Clinical risks
- Genetic risks
- Therapy-related risks

Monitor during and after treatment

- Clinically
- Laboratory
- Imaging

Treat events to reduce complications

Cardiotoxicity: Who?

- Preexisting CVD
- Previous anthracycline chemotherapy
- Poorly controlled risk factors
Genetic risks

- Single nucleotide polymorphism (SNP):
  - rs28714259 SNP, located on Ch 15 in breast cancer patients
  - RARG SNP in pediatric population treated with anthracycline
  - ERBB2 SNP is linked to trastuzumab toxicity

- Still not included in the routine assessment

Cardiotoxic chemotherapeutic agents

<table>
<thead>
<tr>
<th>Chemotherapy agents</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines (dose dependent)</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin (Adriamycin)</td>
<td>3–5</td>
</tr>
<tr>
<td>400 mg/m²</td>
<td>7–26</td>
</tr>
<tr>
<td>550 mg/m²</td>
<td>18–48</td>
</tr>
<tr>
<td>700 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Idarubicin (&gt;90 mg/m²)</td>
<td>5–10</td>
</tr>
<tr>
<td>Epirubicin (&gt;900 mg/m²)</td>
<td>0.9–11.4</td>
</tr>
<tr>
<td>Mitoxanthrone (&gt;120 mg/m²)</td>
<td>2.6</td>
</tr>
<tr>
<td>Liposomal anthracyclines (&gt;900 mg/m²)</td>
<td>2</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>7–28</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td></td>
</tr>
<tr>
<td>&lt;10 g/m²</td>
<td>0.5</td>
</tr>
<tr>
<td>12.5–16 g/m²</td>
<td>17</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>27</td>
</tr>
<tr>
<td>Antimicrotubule agents</td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>2.3–13</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

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<tr>
<th>Chemotherapy agents</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>1.7–20.1%</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1.6–4%</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>0.7–1.2</td>
</tr>
<tr>
<td>Small molecule tyrosine kinase inhibitors</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>2.7–19</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>7–11</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>4–8</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>2–4</td>
</tr>
<tr>
<td>Imatinib mesylate</td>
<td>0.2–2.7</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>0.2–1.5</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>1</td>
</tr>
<tr>
<td>Proteasome inhibitors</td>
<td></td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>11–25</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>2–5</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
Anthracycline toxicity

During administration & Toxicity

<table>
<thead>
<tr>
<th>Acute</th>
<th>Early</th>
<th>Late onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wks to months</td>
<td>Years</td>
<td></td>
</tr>
<tr>
<td>Non-specific ST/T wave changes</td>
<td>HF is common</td>
<td>HF is common High mortality</td>
</tr>
<tr>
<td>Transient LV dysfunction</td>
<td>&lt;1%</td>
<td>0.4-2.1%</td>
</tr>
<tr>
<td></td>
<td>Reversible</td>
<td>5% at 10 yrs</td>
</tr>
</tbody>
</table>

Factors associated with risk of cardiotoxicity following treatment with anthracyclines

Risk factors:
- Cumulative dose
- Female sex
- Age
  - >65 years old
  - Paediatric population (<18 years)
- Renal failure
- Concomitant or previous radiation therapy involving the heart
- Concomitant chemotherapy
  - alkylating or antimicrotubule agents
  - immuno- and targeted therapies
- Pre-existing conditions
  - Cardiac diseases associating increased wall stress
  - Arterial hypertension
  - Genetic factors

*Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin) or anthracenedione (mitoxantrone).

Zamorano et al. EHJ, 2016
Immunotherapies: Trastuzumab

- Concomitant or previous use of anthracycline increases the cardiotoxicity of trastuzumab
- Trastuzumab toxicity typically manifests during treatment
- Usually reversible
- No late onset HF with trastuzumab alone
- Interruption leads to cancer recurrence

Clinical Risk assessment

7 points score Older pts (>67 yrs) at high risk of CVD

Ezaz et al. JAHA, 2014
Risk Prediction Model for Heart Failure and Cardiomyopathy After Adjuvant Trastuzumab Therapy for Breast Cancer

Ezaz et al. JAHA, 2014

<table>
<thead>
<tr>
<th>Risk score</th>
<th>3-year risk of HF/CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>4.5</td>
<td>20-39%</td>
</tr>
<tr>
<td>≥6</td>
<td>≥40%</td>
</tr>
</tbody>
</table>

Ezaz et al. JAHA, 2014

**Baseline assessment**
Clinical, laboratory, Imaging

**Cancer treatment**

**Follow up**
Clinical, laboratory, imaging

**Preserved EF (>50%)**
Repeat assessment during and after ttt

**Impaired EF**
Repeat assessment after 2-3 wks

**Impaired EF**
ACEI/ARBs
BB
Cardiotoxicity: Radiotherapy-induced

- Difficult to evaluate:
  1. Long delay
  2. Concomitant use of cardiotoxic chemotherapeutic agents
  3. Changes in the treated population
  4. Improvement of radiation techniques

- Mechanism: marked interstitial myocardial fibrosis
Prevention of Radiotherapy-induced cardiotoxicity

- Reduction of the radiation dose
- Reduction of the volume exposed
- Deep inspiration breath-holding technique
- CT-based RT planning

Monitoring of patients during and after cancer therapy
Proposed diagnostic tools for the detection of cardiotoxicity

<table>
<thead>
<tr>
<th>Technique</th>
<th>Currently available diagnostic cutoffs</th>
<th>Advantages</th>
<th>Major limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography:</td>
<td>- 1D-based LVEF - 2D Simpson’s LVEF - GLS</td>
<td>• LVES &gt; 10 percentage points decrease to a value below the LLN suggests cardiotoxicity;</td>
<td>• Inter-observer variability.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GLS &gt; 15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.</td>
<td>• Image quality.</td>
</tr>
<tr>
<td>Nuclear cardiac imaging</td>
<td>(MUGA)</td>
<td>• &gt; 10 percentage points decrease in LVEF with a value &lt;50% identifies patients with cardiotoxicity.</td>
<td>• Cumulative radiation exposure.</td>
</tr>
<tr>
<td>Cardiac magnetic resonance</td>
<td></td>
<td>• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderline.</td>
<td>• Limited structural and functional information on other cardiac structures.</td>
</tr>
<tr>
<td>Cardiac biomarkers:</td>
<td>- Troponin I - High-sensitivity Troponin I - BNP - NT-proBNP</td>
<td>• A rise identifies patients receiving antiarrhythmics who may benefit from ACE-i.</td>
<td>• Insufficient evidence to establish the significance of subtle rises.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs further investigation.</td>
<td>• Variations with different assays.</td>
</tr>
</tbody>
</table>

ACE-i = angiotensin converting enzyme inhibiting; BNP = B-type natriuretic peptide; LVEF = left ventricular ejection fraction; LLN = lower limit of normality; NT-proBNP = N-terminal fragment B-type natriuretic peptide.

Zamorano et al. EHJ, 2016

Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

The OVERCOME Trial (prevention of left ventricular dysfunction with Enalapril and Carvedilol in patients submitted to intensive Chemotherapy for the treatment of Malignant Hemopathies)

Xavier Bosch, MD, PhD,‡ Montserrat Rovira, MD, PhD,§ Marta Sitges, MD, PhD,‡ Ariadna Domènech, RN, José T. Ortiz-Pérez, MD, PhD, São Teresa M. de Canals, MD, PhD,‡ Manuel Morales-Ruiz, PhD,‡ Rosario J. Perx, MD, PhD,‡ Mariano Monzó, MD, PhD,‡ Jordi Esteve, MD, PhD,‡

Barcelona, Spain
**Change From Baseline in LVEF in Acute Leukemia Patients Undergoing Chemotherapy in the Intervention and Control Groups**

While no differences were observed in the intervention group, patients in the control group had a 0.7% absolute decrease in their mean left ventricular ejection fraction (LVEF) (p = 0.025), with all but 3 patients having some degree of LVEF reduction. Values are mean ± SEM.

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**Heart failure cardiomyopathy**

**Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol**

Geeta Gulati1,2, Siri Lagethon Heck1,2, Anne Hansen Ree3,4, Pavel Hoffmann5, Jeanette Schulz-Menger6,7, Morten W. Fagerland8, Berit Gravdahug9, Florian von Knobelsdorff-Brenkenhoff9, Åse Bratland10, Trygve H. Storås11, Tor-Arne Hagle11, Helge Røsjø1,2, Kjetil Steine1,2, Jürgen Geisler3,4, and Torbjørn Omland1,2."
Cardiotoxicity in special groups
CVD is the most common complication in survivors of pediatric cancer
- Risk is 8 folds higher
- Lifelong follow up

The 2nd commonly affected group
- Higher incidence with higher CV risk profile
**Pregnant women**

- Insufficient data
- Experimental data: low placental transfer of chemotherapy
- No long-term effects on children born to mothers on chemotherapy during pregnancy

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**When to stop cardiotoxic agents?**
Heart failure

- Reduction of LVEF >10% baseline level to a value less than 50%
- Trastuzumab: interrupted if LVEF <45% or >10% of baseline to levels 45-49%

**To conclude…**

- Cancer patients should be evaluated before starting cancer therapy
- The choice and plan of anti-cancer treatment should depend on the initial cardiac assessment
- Patients should be followed up during and after cancer therapy
Some people who have been treated for breast cancer or lymphoma have a higher risk of developing congestive heart failure than people who haven’t had cancer, results from a new study show. The study researchers retrospectively compared heart failure rates in people who were diagnosed with breast cancer or lymphoma with those in people who did not have cancer. Although the risk of developing heart failure was relatively low overall, people who had been treated for cancer had more than twice the risk of developing heart failure than those who had never had cancer; they found, and the risk was evident as early as one year after their cancer diagnosis. The increased risk persisted for at least 20 years.
Images of venous and arterial thrombi