Cardiotoxicity: Recommendations for Prevention and Therapy

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Disclosures

- None
Cardiotoxicity

- Advances in treatment have led to improved survival of patients with cancer, but have also increased morbidity and mortality due to treatment side effects.
- May be cardiotoxicity from direct effects of the cancer treatment on heart function and structure or may be due to accelerated development of CVD.
- Cardiotoxicity is a very relevant issue in clinical practice, with little evidence based on clinical trials.

Zamarono JL. Eur Heart J 2016
Cardiotoxicity

• Cardio-oncology is growing field
• Many aspects of radiation-induced and cancer drug–induced CVD are still to be fully elucidated

Zamarono JL. Eur Heart J 2016
Cardiotoxicity

- Complicated by inability to predict the long-term consequences of cancer treatment–associated CV side effects leading to under- or overdiagnosis of CVD
  - Results in the failure to prevent adverse events
  - To inappropriate interruption of a potentially lifesaving cancer treatment

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Cardiotoxicity

- Left ventricular dysfunction (LVD) and HF are relatively common and serious side effects of cancer treatment
  - Survivors of pediatric cancer treated with anthracyclines and/or mediastinal radiotherapy have a 15-fold increased lifetime risk for
  - In older patients with CV risk, the short-term risk for developing HF is increased
  - Growing awareness of the occurrence of LVD/HF caused by tyrosine kinase inhibitors

Zamarono JL. *Eur Heart J* 2016
## Risk Factors for Cardiotoxicity

<table>
<thead>
<tr>
<th>Current myocardial disease</th>
<th>Demographic and other CV risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Heart failure (with either preserved or reduced ejection fraction)</td>
<td>• Age (paediatric population &lt;18 years; &gt;50 years for trastuzumab; &gt;65 years for anthracyclines)</td>
</tr>
<tr>
<td>• Asymptomatic LV dysfunction (LVEF &lt;50% or high natriuretic peptide)</td>
<td>• Family history of premature CV disease (&lt;50 years)</td>
</tr>
<tr>
<td>• Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia)</td>
<td>• Arterial hypertension</td>
</tr>
<tr>
<td>• Moderate and severe VHD with LVH or LV impairment</td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>• Hypertensive heart disease with LV hypertrophy</td>
<td>• Hypercholesterolaemia</td>
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<tr>
<td>• Hypertrophic cardiomyopathy</td>
<td></td>
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<tr>
<td>• Dilated cardiomyopathy</td>
<td></td>
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<tr>
<td>• Restrictive cardiomyopathy</td>
<td></td>
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<tr>
<td>• Cardiac sarcoidosis with myocardial involvement</td>
<td></td>
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<tr>
<td>• Significant cardiac arrhythmias (e.g. AF; ventricular tachyarrhythmias)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous cardiotoxic cancer treatment</th>
<th>Lifestyle risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prior anthracycline use</td>
<td>• Smoking</td>
</tr>
<tr>
<td>• Prior radiotherapy to chest or mediastinum</td>
<td>• High alcohol intake</td>
</tr>
<tr>
<td></td>
<td>• Obesity</td>
</tr>
<tr>
<td></td>
<td>• Sedentary habit</td>
</tr>
</tbody>
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Cardiotoxicity

<table>
<thead>
<tr>
<th>Chemotherapy agents</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthraclyclines (dose dependent)</strong></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin (Adriamycin)</td>
<td>3-5</td>
</tr>
<tr>
<td>400 mg/m²</td>
<td></td>
</tr>
<tr>
<td>550 mg/m²</td>
<td>7-26</td>
</tr>
<tr>
<td>700 mg/m²</td>
<td>18-48</td>
</tr>
<tr>
<td>Idarubicin (&gt;90 mg/m²)</td>
<td>5-18</td>
</tr>
<tr>
<td>Epirubicin (&gt;900 mg/m²)</td>
<td>0.9-11.4</td>
</tr>
<tr>
<td>Mitoxantrone &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><strong>Alkylation agents</strong></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>
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<tr>
<td><strong>Antimetabolites</strong></td>
<td></td>
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<tr>
<td>Clofarabine</td>
<td>27</td>
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<tr>
<td><strong>Antimicrotubule agents</strong></td>
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<tr>
<td>Docetaxel</td>
<td>2.3-13</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>&lt;1</td>
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<tr>
<td><strong>Monoclonal antibodies</strong></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>1.7-20.1³&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1.6-4⁴&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>0.7-1.2</td>
</tr>
<tr>
<td><strong>Small molecule tyrosine kinase inhibitors</strong></td>
<td></td>
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<tr>
<td>Sunitinib</td>
<td>2.7-19</td>
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<tr>
<td>Pazopanib</td>
<td>7-11</td>
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<tr>
<td>Sorafenib</td>
<td>4-8</td>
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<tr>
<td>Dasatinib</td>
<td>2-4</td>
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<tr>
<td>Imatinib mesylate</td>
<td>0.2-2.7</td>
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<tr>
<td>Lapatinib</td>
<td>0.2-1.5</td>
</tr>
<tr>
<td>Niotinib</td>
<td>1</td>
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<tr>
<td><strong>Proteasome inhibitors</strong></td>
<td></td>
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<tr>
<td>Carfilzomib</td>
<td>11-25</td>
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<tr>
<td>Bortezomib</td>
<td>2-5</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>&lt;1</td>
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</tbody>
</table>
Anthracycline Toxicity

- Heart damage after anthracycline therapy can be divided into early and late cardiotoxicity
  - Early cardiotoxicity develops during 1st year of anthracycline therapy
  - Late cardiotoxicity refers to damage that only becomes evident < 1 year after the completion of anthracycline therapy
- The risk of developing heart failure remains a lifelong threat

van Dalen EC. *Cochrane Database of Syst Rev* 2011
Anthracycline Toxicity: Frequency

- Widely reported values
- In children:
  - Prevalence of subclinical HF at 6 years after treatment reported >57%
  - Incidence of clinical HF is as high as 16% 5 years after treatment

van Dalen EC. Cochrane Database of Syst Rev 2011
Anthracycline Toxicity

- Anthracyclines, doxorubicin, epirubicin and daunorubicin, are among the most effective drugs used in chemotherapy for cancer patients.
- Mechanism of cardiac damage is unclear.
- Likelihood of toxicity related to the type of anthracycline, the cumulative and the peak dose.

van Dalen EC. Cochrane Database of Syst Rev 2011
Anthracycline Toxicity

- Doxorubicin is associated with a 5% incidence of HF when a cumulative lifetime dose of 400 mg/m² is reached.
- Higher doses lead to an exponential increase in risk, up to 48% at 700 mg/m².

Zamarono JL. *Eur Heart J* 2016
Anthracycline Toxicity

**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

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Prevention of Anthracycline Toxicity

• The meta-analysis for dexrazoxane showed a statistically significant benefit in favor of dexrazoxane for the occurrence of HF

  (RR 0.29, 95% CI 0.20 to 0.41)

• No evidence was found for a difference in response rate or survival between the dexrazoxane and control groups

van Dalen EC. Cochrane Database of Syst Rev 2011
Prevention of Anthracycline Toxicity

Reasonable to use dexrazoxane if the risk of cardiac damage is expected to be high in patients with cancer treated with anthracyclines.

van Dalen EC. *Cochrane Database of Syst Rev* 2011
Immunotherapies and targeted therapies

- Inhibition of HER2 signalling with either antibodies (trastuzumab, pertuzumab) or tyrosine kinase inhibitors (lapatinib) have improved outcomes of patients with HER2-positive breast cancer.
- Initially, cardiotoxicity was high when trastuzumab was given concomitantly with anthracyclines in metastatic breast cancer trials (7-34%).

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Immunotherapies and targeted therapies

• Applying trastuzumab after anthracyclines, or using an anthracycline-free chemotherapy regimen, substantially reduced the rate of clinical HF

• Based on several large-scale trials of adjuvant therapy in breast cancer, all of which prospectively assessed cardiac side effects, the RR for cardiac dysfunction and HF were 5.1% and 1.8%

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Immunotherapies and targeted therapies

- Risk factors for anti-HER2 drug-induced cardiotoxicity include:
  - Previous exposure to anthracyclines
  - Short time (3 weeks vs. 3 months) between anthracycline and anti-HER2 treatment
  - Pre-existing arterial hypertension
  - Low LVEF
  - Older age

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Immunotherapies and targeted therapies

• In contrast to anthracyclines, trastuzumab cardiotoxicity typically manifests during treatment
  – This has led to the implementation of different cardiotoxicity surveillance protocols
• Trastuzumab-associated cardiotoxicity is not believed to be cumulative-dose related
• Trastuzumab-induced LV dysfunction and HF are usually reversible with trastuzumab interruption and/or treatment with HF therapies

Zamarono JL. Eur Heart J 2016
Immunotherapies and targeted therapies

- Treatment interruption of trastuzumab is associated with an increase in cancer recurrence
  - In patients with HER2-positive breast cancer receiving adjuvant trastuzumab, cardiotoxicity was the most common reason for treatment interruption in 13.5% of patients (30% for HF and 70% for asymptomatic LVEF decline)
  - In most trastuzumab breast cancer registration trials, treatment was stopped when patients developed HF or (in asymptomatic patients) when LVEF dropped below 45%

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Immunotherapies and targeted therapies

- There are no randomized trials to prove that HF drugs will improve cardiac function in patients with trastuzumab-associated cardiac dysfunction.

- However, analogous to the experience in patients with anthracycline cardiotoxicity, trastuzumab-associated cardiac dysfunction is likely to improve when these patients are treated with ACE inhibitors.

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Cyclophosphamide Cardiotoxicity

- Cyclophosphamide cardiotoxicity is relatively rare
  - Primarily seen in patients receiving high doses (>140 mg/kg) before bone marrow transplantation
  - HF typically occurs within days of drug administration, and risk factors include total bolus dose, older age, combination therapy with other cancer drugs and mediastinal irradiation

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Platin Cardiotoxicity

• Other alkylating agents such as cisplatin and ifosfamide infrequently cause HF
• Platin-containing chemotherapy requires the administration of a high IVF volume to avoid platin-related toxicity
  – This volume overload in patients with pre-existing myocardial impairment, rather than the direct toxicity of these drugs, is often the cause of first or recurrent episodes of HF

Zamarono JL. Eur Heart J 2016
Prevention of Cardiotoxicity

• Positive health-promoting behavior should be strongly advised:
  – Healthy diet
  – Smoking cessation
  – Regular exercise
  – Weight control

Zamarono JL. *Eur Heart J* 2016
Prevention of Cardiotoxicity

• Aerobic exercise is considered a promising non-pharmacological strategy to prevent and/or treat chemotherapy-induced cardiotoxicity
  – Walking and cycling activities have been tested, and the benefit was greater when the exercise was more intensive, but not until exhaustion

Zamarono JL. Eur Heart J 2016
Monitoring for Cardiotoxicity

- LVEF should be determined before and periodically during treatment for early detection of cardiac dysfunction in patients receiving potentially cardiotoxic chemotherapy using the same method during follow-up.

Zamarono JL. *Eur Heart J* 2016
Monitoring for Cardiotoxicity

• The lower limit of normal of LVEF in echocardiography is 50%--the definition of cardiotoxicity commonly used in registries and trials in patients with cancer

• A patient with a significant decrease in LVEF (>10%), to a value that does not drop below the lower limit of normal, should undergo repeated assessment of LVEF shortly after and during the duration of cancer treatment.

Zamarono JL. Eur Heart J 2016
Monitoring for Cardiotoxicity

- If LVEF decreases >10% to a value below the lower limit of normal (LVEF >50%), ACEi(or ARBs) in combination with beta-blockers are recommended to prevent further LV dysfunction or the development of symptomatic HF, unless contraindicated.
- ACEi (or ARBs) and beta-blockers are recommended in patients with symptomatic HF or asymptomatic cardiac dysfunction unless contraindicated.

Zamarono JL. Eur Heart J 2016
Treatment for Cardiotoxicity: Anthracycline

- In 98% of cases, cardiotoxicity occurred within the first year.
- 11% of patients had full recovery
- 71% patients had partial recovery
- End-chemotherapy LVEF and cumulative doxorubicin dose were independent correlates of cardiotoxicity

Cardinale D. *Circulation* 2015
Conclusions

• Monitoring for symptoms and EF is important
• Healthy lifestyle plays a role
• Interruption of drug therapy important if decline in EF
• Standard of care HF drugs are recommended