Cardio-Oncology: Past Present and Future

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Outline

I. Cardiovascular disease & cancer therapy
   a. The basic
   b. Treatment related cardiovascular diseases
   c. Integrated concept of CVD and cancer

II. The future of Cardio- Oncology
## The longevity of cancer survivors

<table>
<thead>
<tr>
<th>Site</th>
<th>5 years survival</th>
<th>% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1975 (%)</td>
<td>2007 (%)</td>
</tr>
<tr>
<td>Overall</td>
<td>50</td>
<td>67</td>
</tr>
<tr>
<td>Childhood</td>
<td>30</td>
<td>79</td>
</tr>
<tr>
<td>Prostate</td>
<td>67</td>
<td>99</td>
</tr>
<tr>
<td>Breast</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>Colon</td>
<td>51</td>
<td>65</td>
</tr>
<tr>
<td>Lung</td>
<td>12</td>
<td>16</td>
</tr>
</tbody>
</table>
CVD-related Mortality in Early Breast Cancer

Percent Mortality

Years from diagnosis

What is Cardio-Oncology

Cardiovascular Risk factors and diseases

Cancer as a disease

Cancer therapy (past and present)

Treatment related ‘Cardiotoxicity’
# Cancer therapies associated Cardiovascular Toxicities

## Conventional Therapies

<table>
<thead>
<tr>
<th>Cytotoxic</th>
<th>Hormonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Androgen deprivation therapy</td>
</tr>
<tr>
<td>Doxorubicin, daunorubicin, epirubicin, Idarubicin</td>
<td>Bicalutamide, enzalutamide, abiterone</td>
</tr>
<tr>
<td>Fluoropyrimidines</td>
<td>Antiestrogen</td>
</tr>
<tr>
<td>5-fluorouracil, capecitabine, gemcitabine</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Microtubules inhibitors</td>
<td>Docetaxel, paclitaxel</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td></td>
</tr>
<tr>
<td>Cisplatin, cyclophosphamide</td>
<td></td>
</tr>
</tbody>
</table>

## Novel (Targeted Therapies)

<table>
<thead>
<tr>
<th>Signaling Pathways</th>
<th>Other targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HER-2</td>
<td>Proteosome Inhibitors</td>
</tr>
<tr>
<td>Trastuzumab Pertuzumab</td>
<td>Bortezumib</td>
</tr>
<tr>
<td>Lapatinib</td>
<td></td>
</tr>
<tr>
<td>VEGF signaling</td>
<td>Immunomodulators</td>
</tr>
<tr>
<td>Bevacizumab, Ramucirumab</td>
<td>Thalidomide, lenalidomide</td>
</tr>
<tr>
<td>Sunitinib, Sorafenib, Axitinib, Regorafenib, Vandetanib</td>
<td></td>
</tr>
<tr>
<td>Anti-BCR-ABL TKIs</td>
<td>HDAC inhibitors</td>
</tr>
<tr>
<td>Imatinib, crizotinib, dasatinib vemorafenib etc...</td>
<td>Vorinostat, Depsipeptide</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>Others</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Asenic</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td></td>
</tr>
</tbody>
</table>
Spectrum of Cardiotoxicity

### Spectrum of Cardiotoxicities

#### Conventional Therapies

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<tr>
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</table>
| Anthracyclines  
Cardiomyopathy, Heart failure | Androgen deprivation therapy  
Metabolic syndrome, VTE |
| Fluoropyrimidines  
Myocardial ischemia (reversible), Tachycardia | Anti-estrogen VTE |
| Microtubules inhibitors  
Arrythmias | |
| Alkylating agents  
Myocardial ischemia | |

#### Novel (Targeted Therapies)

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| Anti-HER-2  
Cardiomyopathy  
Heart failure | Proteosome Inhibitors  
Arrythmia  
Hypertension |
| VEGF signaling  
Hypertension  
VTE  
Hemorrhage | Immunomodulators  
VTE |
| Anti-BCR-ABL TKIs  
Pulmonary hypertension  
Pericardial effusion | HDAC inhibitors  
Hypertension  
Dyslipidemia  
Cardiomyopathy |
| mTOR inhibitors  
Hypertension  
Myocardial ischemia | Other  
Asenic – QTc prolongation |
Molecular mechanism of toxicity for targeted therapy
Left Ventricular Dysfunction

• Mechanism of toxicity

• LV dysfunction
  • Type I: anthracycline associated with radical species resulting in structural abnormality, apoptosis.
  • **Type II:** related to targeted therapy targeting Erb2 (HER2) causing mitochondria apoptosis resulting in failure of myofibril contractile element. Likely to be reversible if offending agents discontinued

Hypertension

• **Mechanism of toxicity**
  
  • Usually occurs within the first few weeks after therapy initiated
  • Associated with anti-VEGF
  • VEGF is known to increase the synthesis of nitric oxide (NO)
  • Therefore, decreased level of endogenous NO causing vasoconstriction
  • Also, up-regulation of baroreceptor function and increased vascular tone
  • May be an indicator of efficacy

Hemorrhagic Events/VTE

• Mechanism of toxicity
  • Associated with VEGF pathway
  • Nitric oxide (NO) maintains the integrity of endothelial cells
  • Activate platelets aggregation and degranulation to trigger thrombosis when drugs bind to Fc RII receptor
• Risk factors included
  • Elderly
  • Past medical history of diabetes
  • Dose intensity

Risk factors to cardiovascular toxicities

- Baseline CV diseases
- Age (≥ 50 years old for trastuzumab, ≥ 65 years old for anthracyclines)
- Family history of premature CV disease
- Diabetes, dyslipidemia, hypertension
- Smoking
- Obesity
- Prior cancer therapy history (e.g. radiation or pre-exposure to anthracyclines)
- Advanced cancer
- Site of cancer (for thromboembolism)
- Impaired organ function
- Concomitant drugs
- Alcohol consumption
Strategies to reduce toxicities

All cancer treatment
- Identify and treat risk factors/comorbidities
- Avoid drugs to potentiate CV toxicities e.g. QT prolonging agents
- Minimize irradiation
- Monitoring protocol

Anthra cyclines
- Limit life time accumulating dose
- Alter delivery system/formulation
- Antidote (dexrazoxane)
- CHF management
Strategies to reduce toxicities

- **Trastuzumab**
  - Reversible cardiomyopathy
  - CHF management

- **Immuno modulators**
  - Risk VS benefit of bleeding VS embolism
  - Antiplateletes or anticoagulation

- **VEGF inhibitors/TKIs**
  - Baseline blood pressure
  - Hypertension management
Challenges in Cardio-Oncology

- Most data are from cancer clinical trials that excluded patients with history of CVD and metabolic disorders
- Toxicities assessments stop after drug discontinuation
- Toxicities can appear late and/or intermittently
- Essential to distinguish between treatment-related CVD and treatment – independent metabolic adverse effects
To sum up

• Increased number of cancer survivors worldwide
• Conventional and novel cancer treatments are associated with cardiovascular toxicities
• Baseline risk factors must be evaluated prior to initiate treatment
• Monitoring and better standardized assessment will help minimize CVD-associated cancer care