Cardio-Oncology: Cardiologist’s Perspective

Srisakul Chirakarnjanakorn, MD
Siriraj Hospital
Mahidol University

Agenda

- Introduction
- Mechanisms of cardiotoxicity
- Definition and Diagnosis
- Monitoring cardiotoxicity
- Management
Introduction:
How important is cardio-oncology?

- Cancer-related death is one of the leading causes of death.
- Over the past few decades, mortality from cancer has decreased tremendously due to earlier diagnosis and novel treatments.
- Cardiac morbidity and mortality of cancer survivors has increased.
- Risk of death from cardiovascular causes exceeds that of tumor recurrence for many forms of cancer.
Cardio-Oncology
CV complications related to chemotherapy and radiation therapy
- Myocyte damage
- Left ventricular dysfunction and heart failure
- Thrombogenesis
- Ischemia and vasospasm
- Pericardial pathology
- Hypertension
- Conduction and rhythm disturbances

Long-Term Survival: Underlying Cause of Cardiomyopathy
3.5-fold increased mortality risk compared with idiopathic cardiomyopathy

Felker, GM. NEJM 2000
**Agenda**

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**Cancer Therapy Related to Cardiotoxicity**

- **Cytotoxic chemotherapy**
  - Anthracyclines: doxorubicin, daunorubicin, epirubicin, and idarubicin
  - Alkylating agents: cyclophosphamide, ifosfamide, and melphalan
  - Microtubular Polymerization Inhibitors/Taxanes: paclitaxel and docetaxel

- **Molecular targeted therapy**
  - HER2-Targeted Cancer Therapies: Trastuzumab
  - VEGF Inhibitors: Tyrosine Kinase Inhibitors (sunitinib, sorafenib)

- **Chest and mediastinal irradiation**
Cancer Therapy Related to Cardiotoxicity

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Anthracyclines: Cardiotoxicity

- Association between cumulative dosing and cardiotoxicity:
  - Diastolic dysfunction: 200 mg/m²
  - Systolic dysfunction: 400-600 mg/m²
- LV dysfunction can occur at any dose:
  - 18.9% of patients receiving a doxorubicin dose of 240 mg/m² in combination with cyclophosphamide
- Risk factors: CVD risk factors, mediastinal irradiation, concomitant therapy with agents eg. cyclophosphamide, paclitaxel and trastuzumab


Cumulative incidence of AC related cardiotoxicity

Anti-HER2

HER2/ERbB2 receptor expressed on myocytes and plays a protective role against myocardial stress

Prevalence: adjuvant therapy to anthracycline based regimen
- Heart failure: 1.7-4.1%
- LV dysfunction in 7.1-18.6% of

Trastuzumab (humanized anti-HER2 monoclonal antibody)
### CTRCD type I vs. type II

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic agent</strong></td>
<td>May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress</td>
<td>High likelihood of recovery (to or near baseline cardiac status) in 5-4 months after interruption (irreversible)</td>
</tr>
<tr>
<td>Clinical course and typical response to antiremodeling therapy (β-blockers, ACE inhibitors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose effects</strong></td>
<td>Cumulative, dose related</td>
<td>Not dose related</td>
</tr>
<tr>
<td>Effect of rechallenge</td>
<td>High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death</td>
<td>Increasing evidence for the relative safety of rechallenge (additional data needed)</td>
</tr>
<tr>
<td>Ultrastructure</td>
<td>Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)</td>
<td>No apparent ultra structural abnormalities (though not thoroughly studied)</td>
</tr>
</tbody>
</table>

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### Chest/Mediastinal Irradiation

- **Acute radiation myocarditis:** rare
- **Late to very later complications:**
  - Macrovascular complications
  - Microvascular complications
  - Endothelial injury: valvular dysfunction
  - Atherosclerosis
  - Fibrosis
  - Pericardial disease: constrictive pericarditis

_Bloom MK, Circ HF 2016_
Chest/Mediastinal Irradiation
Late to very late complications

- In patients with breast cancer, received chest RT: Events occurred 5 years after initial exposure and continued through the third decade following exposure.
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### Chemotherapy related cardiac dysfunction (CTRCD)

**No Specific Definition!**

- Anthracycline cardiotoxicity:  
  - >20% decrease in LVEF when baseline LVEF is normal, or  
  - >10% decrease when baseline LVEF is not normal

- Trastuzumab cardiotoxicity:  
  - Asymptomatic decrease in LVEF of >10% to <55%, or  
  - Decrease in LVEF of >5% to <55%, combined with symptoms of heart failure

- Decrease in LVEF >10%, to a value < 53%  
  
  US FDA 2015

US FDA 2015

US FDA 2015

J Clin Oncol. 2002;20:1215–1221

US FDA 2015

Chemotherapy related cardiac dysfunction: Diagnosis

- Clinical CTRCD:
  - LVEF measured by cardiac imaging:
  - Echo, MUGA, MRI, PET/MRI etc.

- Subclinical CTRCD:
  - Global longitudinal strain
  - Serum troponin-I
Inter-measurement variability
- Intra-observer variability
- Inter-observer variability
- Test-retest variability:
  Temporal variability
  Coefficient of variation

Temporal variability (Coefficient of variation; COV)

<table>
<thead>
<tr>
<th>Method</th>
<th>EF COV (95% CI), %</th>
<th>EDV COV (95% CI), %</th>
<th>ESV COV (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bi-Plane</td>
<td>7.4 (6.2 – 9.1)</td>
<td>16.2 (13.7 – 20.0)</td>
<td>22.0 (18.5–27.0)</td>
</tr>
<tr>
<td>Bi-Plane + Contrast</td>
<td>8.4 (7.0 – 10.5)*</td>
<td>16.0 (13.3 – 20.0)</td>
<td>23.6 (19.7 – 29.6)</td>
</tr>
<tr>
<td>Triplane</td>
<td>9.4 (7.9 – 11.5)</td>
<td>23.0 (19.4 – 28.2)*</td>
<td>26.2 (22.1 – 32.3)</td>
</tr>
<tr>
<td>Triplane + Contrast</td>
<td>9.4 (7.8 – 11.8)</td>
<td>20.1 (16.7 – 25.2)</td>
<td>23.6 (19.7 – 29.7)</td>
</tr>
<tr>
<td>3D</td>
<td>4.0 (3.3 – 4.9)</td>
<td>11.9 (10.0 – 14.7)</td>
<td>13.2 (11.1 – 16.2)</td>
</tr>
<tr>
<td>3D + Contrast</td>
<td>7.2 (6.0 – 9.1)*</td>
<td>16.6 (13.8 – 20.9)*</td>
<td>20.0 (16.5 – 25.1)*</td>
</tr>
</tbody>
</table>

Non-contrast 3D had the lowest temporal variability based on COV for EF, EDV, and ESV compared to all other methods (p<0.01 for all). *statistically different when compared to the respective non-contrast method (p<0.05).
Temporal variability of EF, EDV, ESV

Minimal detectable change in LVEF not attributable to variability: 5-6% with 3D TTE vs. 10-13% with 2D TTE

Multi-gated acquisition (MUGA) scan

- Advantages
  - Excellent reproducibility
  - Not dependent on acoustic windows
  - Historical outcome data

- Disadvantages:
  - Ionizing radiation
    - 5-10 mSv per scan
  - No additional info on pericardium, valves and RV
Chemotherapy related cardiac dysfunction: Diagnosis

- Clinical CTRCD:
  - LVEF measured by cardiac imaging:
  - Echo, MUGA, MRI, PET/MRI etc.

- Subclinical CTRCD:
  - Global longitudinal strain
  - Serum troponin-I

Table 3 Percent changes in echocardiographic parameters in 6 months within the groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No cardiotoxicity</th>
<th>Cardiotoxicity</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS</td>
<td>0.2 ± 8.6</td>
<td>11.4 ± 9.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GLSR-S</td>
<td>−0.2 ± 16.8</td>
<td>12.8 ± 19.4</td>
<td>.009</td>
</tr>
<tr>
<td>GLSR-E</td>
<td>5.1 ± 21.2</td>
<td>−11.9 ± 14.5</td>
<td>.002</td>
</tr>
<tr>
<td>s'</td>
<td>−5.0 ± 18.9</td>
<td>−17.0 ± 23.9</td>
<td>.04</td>
</tr>
<tr>
<td>e'</td>
<td>3.5 ± 37.1</td>
<td>−10.0 ± 28.7</td>
<td>.09</td>
</tr>
<tr>
<td>GCS</td>
<td>−1.0 ± 29.7</td>
<td>9.3 ± 27.4</td>
<td>.18</td>
</tr>
<tr>
<td>GRS</td>
<td>8.3 ± 48.5</td>
<td>−10.0 ± 39.3</td>
<td>.11</td>
</tr>
</tbody>
</table>

GCS, Global circumferential peak systolic strain; GRS, global radial peak systolic strain.
Change in GLS at 6 months: AUC = 0.84, p<0.001
Optimal cut point = 11% reduction (95% CI, 8.3%–14.6%) having sensitivity of 65% and specificity of 94%.

NRI 0.77 (95% CI, 0.33–1.22; P = .036)
IDI 18.6% (95% CI, 8.6–28.6; P = .0003).

2014 ASE guideline: GLS
Subclinical CTRCD:
- A relative percentage decrease of >15% compared with baseline, or
- Absolute value <19% if no baseline
Strain imaging

Table 5: Effect of vendor age and gender on GLS

<table>
<thead>
<tr>
<th>Vendor</th>
<th>0–19</th>
<th>20–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60+</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>-22.1 ± 2.4</td>
<td>-21.2 ± 1.9</td>
<td>-21.1 ± 2.1</td>
<td>-21.4 ± 2.0</td>
<td>-21.0 ± 2.2</td>
<td>-20.3 ± 1.9</td>
<td>.0218</td>
</tr>
<tr>
<td>Male</td>
<td>-21.7 ± 3.1</td>
<td>-20.9 ± 1.9</td>
<td>-20.6 ± 1.9</td>
<td>-20.9 ± 1.8</td>
<td>-21.0 ± 1.9</td>
<td>-19.7 ± 1.4</td>
<td>.1962</td>
</tr>
<tr>
<td>Female</td>
<td>-22.4 ± 1.6</td>
<td>-22.3 ± 1.6</td>
<td>-22.8 ± 1.8</td>
<td>-22.6 ± 2.1</td>
<td>-23.3 ± 1.9</td>
<td>-20.9 ± 2.1</td>
<td>.0348</td>
</tr>
<tr>
<td>P (male vs female)</td>
<td>.0296</td>
<td>.0001</td>
<td>.0178</td>
<td>.0029</td>
<td>.1381</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>-19.9 ± 2.5</td>
<td>-19.0 ± 2.1</td>
<td>-19.5 ± 2.2</td>
<td>-18.2 ± 2.5</td>
<td>-17.6 ± 2.5</td>
<td>-18.7 ± 2.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Male</td>
<td>-19.4 ± 2.7</td>
<td>-18.8 ± 2.0</td>
<td>-19.1 ± 2.3</td>
<td>-17.9 ± 2.8</td>
<td>-16.9 ± 2.3</td>
<td>-15.8 ± 1.4</td>
<td>.0019</td>
</tr>
<tr>
<td>Female</td>
<td>-20.5 ± 2.2</td>
<td>-20.6 ± 2.3</td>
<td>-20.2 ± 2.0</td>
<td>-19.3 ± 0.9</td>
<td>-20.4 ± 1.5</td>
<td>-17.3 ± 2.3</td>
<td>.0002</td>
</tr>
<tr>
<td>P (male vs female)</td>
<td>.1349</td>
<td>.0248</td>
<td>.1083</td>
<td>.4316</td>
<td>.0294</td>
<td>.0028</td>
<td></td>
</tr>
<tr>
<td>V3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>-18.7 ± 2.6</td>
<td>-18.3 ± 3.1</td>
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<tr>
<td>Female</td>
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<td>-20.2 ± 2.4</td>
<td>-20.4 ± 2.8</td>
<td>-19.7 ± 1.8</td>
<td>-18.3 ± 2.8</td>
<td>-18.6 ± 2.3</td>
<td>.0141</td>
</tr>
<tr>
<td>P (male vs female)</td>
<td>.0076</td>
<td>.9787</td>
<td>.9201</td>
<td>.1415</td>
<td>.7374</td>
<td>.0068</td>
<td></td>
</tr>
</tbody>
</table>

V1, Vivid 7 or Vivid E9 (GE Healthcare); V2, IE33 (Philips Medical Systems); V3, Artida or Apex (Toshiba Medical Systems).
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Chemotherapy related cardiac dysfunction: Diagnosis

- Clinical CTRCD:
  - LVEF measured by cardiac imaging:
  - Echo, MUGA, MRI, PET/MRI etc.

- Subclinical CTRCD:
  - Global longitudinal strain
  - Serum troponin-I
Cardiac biomarkers: Troponin-I

Screening:
- Absence of troponin elevation in patients receiving high-dose anthracyclines: High NPV for CTRCD
- Troponin I levels at completion of anthracycline treatment: predict of subsequent reduction in LVEF and cardiac events

Risk stratification, monitoring:
- Increased troponin I in patients receiving trastuzumab:
  - Decrease likelihood of LVEF recovery
  - Higher incidence of cardiac events

Predictive value of Troponin change: LVEF reduction

Predictive value of Troponin change: Cardiac event free rate

Cardiac biomarkers: Concerns

- No specific strategy:
  - Timing of measurement?:
    - How often, timing relative to chemo
    - When can we stop checking?
  - Optimal assays?
  - Use alone or in conjunction with cardiac imaging?
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Management

- Prevention strategy:
  - Primary prevention
  - Secondary prevention

Secondary prevention

- Standard neurohormonal blockade for heart failure management: ACEI/ARB, Beta-blocker, MRA?
  - Lack of large RCT
Secondary prevention: Asymptomatic LVD

Table 2. Treatment of ASLVD in Adult Patients with Cardiotoxic Chemotherapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>Patient Population</th>
<th>N</th>
<th>Cardiac Treatment Modality</th>
<th>Timing of Treatment</th>
<th>Mean Follow-Up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardale et al19</td>
<td>Prospective</td>
<td>201 patients with LVEF ≤ 50% due to anthracyclines</td>
<td>201</td>
<td>Enalapril up to 20 mg/d and concomitant use of furosemide 10 mg/d</td>
<td>Baseline immediately after initiation of ASLVD</td>
<td>Echo at baseline, every month for 3 mo, and every 3 mo during follow-up 3 y, every 6 mo thereafter</td>
<td>Mean follow-up 36 mo</td>
</tr>
<tr>
<td>Cardale et al19</td>
<td>Prospective</td>
<td>Mix of cancer, non-Hodgkin's lymphoma, Chemotherapy naïve patients scheduled for anthracyclines (note excluded high doses of anthracycline or taxanes)</td>
<td>2625</td>
<td>Enalapril alone (before 1999) and furosemide 10 mg/d</td>
<td>Baseline, every 3 mo during chemotherapy, every 3 mo during first year following chemotherapy, every 6 mo during the following 4 y, yearly afterward</td>
<td>Echo at baseline, every 3 mo during chemotherapy, at end of treatment (within 1 mo, every 3 mo during first year following chemotherapy, every 6 mo during the following 4 y, yearly afterward)</td>
<td>Mean follow-up 3.5 y</td>
</tr>
</tbody>
</table>

ASLVD indicates asymptomatic left ventricular dysfunction; EP: end point; LVEF, and left ventricular ejection fraction. *Responders had a significantly shorter time to initiation of therapy.

Percentage of Responders vs Time to start HF therapy

![Graph showing percentage of responders vs time to start HF therapy]

Percentage of LVEF change vs Time to start HF therapy

Cardiac event rate

Responders:
LVEF increased ≥ 50%

Partial responders:
LVEF increased ≥10% (absolute points) but <50%

Nonresponders:
LVEF increased <10% (absolute points) and <50%.
Primary prevention

- Carvedilol and nebivolol started at initiation of anthracycline use: higher degree of LVEF preservation

- Use of β-blockers during treatment with trastuzumab and anthracyclines was associated with a lower incidence of HF over a 5-year period.

- Controversial results of benefit of ACEI on CTRTD

Thank you for your kind attention

srichcardio@gmail.com
srisakul.chi@mahidol.ac.th