Breast Cancer and Cardiotoxic Chemotherapy and Radiotherapy

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Female patient, age 75 y, with occult colorectal carcinoma and ischemic heart disease

Depending on whether the patient first sees:

**Oncologist:**
- Detects fecal blood
- Colonoscopy reveals tumor
  - Surgery, FOLFOX+Bevacizumab
  - 5-FU induced cardiotoxicity
  - Thrombosis, hypertension
  - Progressive heart failure - Cardiac insufficiency

**Cardiologist:**
- Finds ischemic heart disease
  - Medical therapy and cardiac monitoring
  - GI tract bleeding
  - Colon cancer detected
  - Liver metastases
  - Chemotherapy with heart monitoring - Metastatic disease

**Cardio-Oncologist**
- Prevention of Metastasis and HF
Outline

- Cardiotoxic agents
- Biomarkers
- Preventative strategies
- Follow up
Classification

- Type 1
  - Cumulative-doses related
  - Irreversible, cell death
  - Typical biopsy changes
  - Doxorubicin is the model

- Type 2
  - Not cumulative-dose related
  - Predominately reversible, cell dysfunction
  - Absence of anthracycline-like biopsy changes
  - Trastuzumab
Anthracyclines (doxorubicin)

- Dose dependent risk of cardiotoxicity
- Immediate damage to myocardial cells by free radical generation
- Can be early, late or post-treatment
- Cardiomyopathy and heart failure most common concern of toxicity
- Can be treated
- Cell death cannot be reversed
- Agents that increase toxicity
  - Paclitaxel
  - Trastuzumab
Antracycline Cardiotoxicity

Risk Factors
- Age > 70
- HTN
- Hx CAD
- Female sex
- Previous irradiation
- Previous antracycline

Cumulative doxorubicin dosing
- 240 mg/m²: asymptomatic decline in EF
- 400 mg/m²: 5.1% CHF incidence
- 500 mg/m²: increased toxicity

Side Effects
- Acute
  - Pericarditis
  - Myocarditis
  - LV dysfunction
  - Arrhythmias
- Delayed
  - CHF
Taxanes: Paclitaxel

- Interferes with metabolism and excretion of antracyclines
- Acute asymptomatic bradycardia, 30%
- Serious arrhythmia, MI
- Decreased cardiotoxicity when combined with D
  - Slow infusion of both or increased time between them
  - Cumulative doxorubicin dose <360 mg/m², D– T
- Less of an issue with epirubicin
- Newer taxane agents
Trastuzumab

- Humanized monoclonal antibody
- Approved for treatment of HER2 overexpressing breast cancer
  - Approximately 25% to 30% of breast cancer cases
  - Associated with poorer prognosis
- Incidence of cardiac dysfunction and CHF 2-5%
  - Adjuvant T cardiotoxic when given concomitantly with paclitaxel after AC
  - The long-term impact of trastuzumab-induced cardiotoxicity unclear, likely less severe than anthracycline-induced cardiotoxicity

Trastuzumab

- Mechanism for trastuzumab-induced cardiac dysfunction is different from doxorubicin
  - Typically reversible
  - When used following an anthracycline, the damage constitutes a sequential stress
  - Best option to limit initial anthracycline damage

- Animal testing suggests HER2 signaling in cardiac myocytes is important to prevent dilated cardiomyopathy

- Optimal duration of T unknown

- Asymptomatic declines in LV EF common

- Not dose dependent

- Risk factors: age, HTN, BMI, previous LV dysfxn

Radiation

- **Acute:** pericarditis, pericardial effusion, arrhythmias
  - Leads to myocyte ischemia and fibrosis
- **Delayed:** constrictive pericarditis
- Coronary endocyte damage leads to inflammation and then atherosclerosis
- Current radiotherapy focused, less radiation
Biomarkers

- Natriuretic peptides to detect cardiotoxicity
- 27 patients on anthracyclines, serial BNP and echo
- BNP elevations after AC administration, cardiac tolerance to the agent
- Persistent elevation of BNP: poor prognosis
- A/E ratio correlated with increased BNP levels, may suggest diastolic dysfunction
- “Diagnosis of degree of cardiac tolerance by response to drug administration may be analogous to use of stress testing (exercise) to help define underlying left ventricular dysfunction.”

LVEF percentage changes during the follow-up in TnI+ (squares) and TnI– (circles) patients.
Troponin I is valuable in detecting Cardiotoxicity

**TABLE 3. Cardiac Events In the Study Groups**

<table>
<thead>
<tr>
<th>Event</th>
<th>Total (n=703)</th>
<th>Tnl−/− (n=495)</th>
<th>Tnl+/− (n=145)</th>
<th>Tnl+/+ (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death</td>
<td>3 (0.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (0.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>3 (0.4)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>47 (7)</td>
<td>1 (0.2)</td>
<td>18 (12)</td>
<td>28 (44)</td>
</tr>
<tr>
<td>Asymptomatic left ventricular dysfunction</td>
<td>37 (5)</td>
<td>2 (0.4)</td>
<td>24 (17)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Life-threatening arrhythmias</td>
<td>17 (2)</td>
<td>2 (0.4)</td>
<td>10 (7)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Conduction disturbances requiring pacemaker implantation</td>
<td>2 (0.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Cumulative events</strong></td>
<td>111 (16)</td>
<td>5 (1)</td>
<td>53 (37)*</td>
<td>53(84)*†</td>
</tr>
</tbody>
</table>

Values are given as n (%).
*P<0.001 vs Tnl−/− group; †P<0.001 vs Tnl+/− group.
How to Reduce Anthracycline Cardiotoxicity

- Limit cumulative dose
  - Expression of cardiotoxicity unusual at cumulative doses < 300 mg/m$^2$

- Modification of dose schedule
  - Weekly administration or every 2 weeks

- Use continuous rather than rapid infusion

- Liposomal delivery systems
Prevention of Anthracyclin-induced Cardiotoxicity

- Dexrazoxane—EDTA derivative
  - Given during antracycline infusion
  - Decreases oxidized iron levels in myocytes
  - Use when cumulative anthracycline doses of at least 300 mg/m²
  - Can reduce anticancer effect of anthracyclines
  - Increase thrombocytopenia and granulocytopenia
  - Improved survival seen in some studies
    - Unclear if improvement due to improved cardiac status
  - Can worsen thrombocytopenia and granulocytopenia
Comparison of left ventricular ejection fraction (EF) at baseline (black bars) and after adriamycin chemotherapy (white bars) in the 2 groups.

Kalay, N. et al. J Am Coll Cardiol 2006;48:2258-2262
Individual change in mitral early/late diastolic flow (E/A) ratio before and after chemotherapy (CT) in the 2 groups

Kalay, N. et al. J Am Coll Cardiol 2006;48:2258-2262
Figure 1. LVEF at baseline and during the 12-month follow-up in control subjects (left) and the ACEI group (right) in patients with (□) or without (•) persistent TnI increase.

Cardinale D et al. Circulation 2006;114:2474-2481

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### ACE-I: prevention of toxicity

Cardinale D et al. Circulation. 2006;114:2474-2484

<table>
<thead>
<tr>
<th>Event</th>
<th>Total (n=114), n (%)</th>
<th>ACEI Group (n=56), n (%)</th>
<th>Control Subjects (n=58), n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>0.49*</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td>4 (7)</td>
<td>0.07*</td>
</tr>
<tr>
<td>Heart failure</td>
<td>14 (12)</td>
<td>0 (0)</td>
<td>14 (24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arrhythmias requiring treatment</td>
<td>11 (10)</td>
<td>1 (2)</td>
<td>10 (17)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cumulative events</td>
<td>31</td>
<td>1</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Fisher exact test.*
Reversibility of LV dysfunction

<table>
<thead>
<tr>
<th>Physical status</th>
<th>LVEF</th>
<th>Trastuzumab</th>
<th>LVEF monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>↓ but normal&lt;br&gt;↓ &gt; 10 points but normal&lt;br&gt;↓ 10-20 points and LVEF &gt; 40%</td>
<td>Continue&lt;br&gt;Continue&lt;br&gt;Continue</td>
<td>Repeat in 4 weeks&lt;br&gt;Repeat in 4 weeks&lt;br&gt;Repeat in 2 to 4 weeks</td>
<td>Consider β-blockers&lt;br&gt;Treat for CHF</td>
</tr>
<tr>
<td></td>
<td>↓ &gt; 20 points to &lt; 40% or LVEF &lt; 30%</td>
<td>Hold</td>
<td>Repeat in 2 weeks</td>
<td>Treat for CHF</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>↓ &lt; 10 points&lt;br&gt;↓ &gt; 10 points and LVEF &gt; 50%</td>
<td>Continue&lt;br&gt;Continue</td>
<td>Repeat in 2-4 weeks&lt;br&gt;Stable or improved: continue trastuzumab</td>
<td>Search for noncardiac pathology (e.g., anemia)&lt;br&gt;Treat for CHF</td>
</tr>
<tr>
<td></td>
<td>↓ &lt; 30 points</td>
<td>Stop</td>
<td></td>
<td>Treat for CHF</td>
</tr>
</tbody>
</table>
Proposal for Imaging

Thorough cardiac assessment including baseline LVEF, before starting treatment
Reassessment after 300 mg/m² of doxorubicin or equivalent; after every one to two cycles if additional anthracycline is given
Follow-up LVEF measurements: 3–6 months following completion of therapy and then yearly for 5 years
Higher risk individuals, especially if LVEF has decreased >15% from baseline or to <45%, may be monitored more frequently
In case of anthracycline-related cardiomyopathy at any time during or following treatment, further anthracycline should be avoided (or after careful consideration of the risks)
In patients with comorbidities or diagnostic findings at risk for cardiotoxicity, anthracycline-free adjuvant chemotherapy can be considered, particularly if additional therapy with targeted agents is planned
If potentially cardiotoxic treatment is indicated, all other sources of oxidative stress should, whenever possible, be avoided and volume status optimized

Harbeck et al,
Conclusions

- Chemotherapeutic agents have cardiotoxicities.
- Close monitoring for symptoms and signs of CHF need to be performed in addition to echocardiographic monitoring.
- Preventative measures exist.
- Balance of cardiac and oncologic risks need to be taken into account.