Cardio-Oncology: changing the course of cancer and heart disease

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Disclosures

 Bayer Pharmaceuticals: clinical trial investigator

Objectives

 The learner will develop a better understanding of how cardiology and oncology intersect to improve both oncologic and cardiovascular outcomes for patients.
 The learner will have a basic approach to understanding the cardiotoxicity of common chemotherapy agents and how to surveil and manage these toxicities.

First and foremost, why is this important???

 Cancer and cardiac disease remain the two most common disease states in the developed world.
 Cardiac disease may exist already in many of our cancer patients needing treatment.
 Cardiac complications can develop from the use of multiple cancer treatment modalities.
 Undertreatment of either condition can have significant and long lasting complications for patients.

Two of my patients…

 SK is an 19 y/o girl diagnosed with APML (AML M3) in May of 2015.
 Treated with cytarabine, daunorubicin (total cumulative dose 500mg/m2) followed by ATRA (retinoid).
 Issues: developed ATRA differentiation syndrome and SAH but ultimately was able to continue. Started maintenance ATRA in 11/2015.
 In complete morphologic, molecular and cytogenetic remission.

SK continued

 Hospitalized end of December with possible PNA.
 Ultimately diagnosed with fulminant biventricular heart failure.
 Needed inotropes and IABP. Ultimately received HM2 LVAD and percutaneous RVAD.
 Discharged after 4 weeks on milrinone and HM2.
 Weaned milrinone completely in 4 weeks.
 What next???
Next patient

R.C. is a 42 y/o woman with left intraductal breast cancer
PMH: HTN, morbid obesity
(Her-2/ neu+/ progesterone +, Estrogen -)
s/p lumpectomy, XRT and adjuvant traztuzumab and Tamoxifen in 2012. After 7/12 doses, MUGA dropped from 56% to 44%. Continued tamoxifen.

Patient 2

Echo in 8/2015: LVEF 55% (probably overestimate). No strain done. Pertuzuzamab and traztuzumab started.
Echo 12/2015: LVEF lower with a possible wall motion abnormality. Can’t due strain due to image quality. Asymptomatic except fatigue.
CT heart 1/2016: nonobstructive CAD, LVEF 48% and incidental RLL PE. Low normal RVEF.
What to do next?????

Pathophysiology of cardiac toxicity from various chemotherapeutics and role of preventative therapies.

<table>
<thead>
<tr>
<th>Characteristic agent</th>
<th>Type I (myocardial damage)</th>
<th>Type II (myocardial dysfunction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical course, response to CRCD therapy</td>
<td>May stabilize, but underlying damage may persist and recur, even in patients in remission at zero</td>
<td>High likelihood of recovery (to or near baseline cardiac status) in 2-4 months (reversible)</td>
</tr>
<tr>
<td>New effects</td>
<td>Cardiac remodeling, relative heart failure</td>
<td>No new effect</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Free radical formation, oxidative stress/damage</td>
<td>Blocked ErbB2 signaling</td>
</tr>
<tr>
<td>Noninvasive cardiac testing</td>
<td>Decreased ejection fraction by ultrasound or nuclear determination: global decrease in wall motion</td>
<td>Decreased ejection fraction by ultrasound or nuclear determination: global decrease in wall motion</td>
</tr>
<tr>
<td>Effect of rechallenge</td>
<td>High likelihood of recurrent dysfunction that is unresponsive to treatment, can result in intractable heart failure and death</td>
<td>Increasing evidence for the relative safety of rechallenge, additional data needed</td>
</tr>
<tr>
<td>Effect of late sequential stress</td>
<td>High likelihood of sequential stress-related cardiac dysfunction</td>
<td>Low likelihood of sequential stress-related cardiac dysfunction</td>
</tr>
</tbody>
</table>

Who are the culprits?

Risk Assessment and Monitoring
Assessing CV risk for oncologic treatment

- Is there pre-existing cardiovascular disease or risk factors?
- Is there a plan for known cardio-toxic agents as part of the regimen?
- Did the patient develop new cardiac symptoms during treatment for cancer?
- What is the therapeutic goal of treatment: curative v palliative?
- What are the patient’s goals of care?

A Structured Team

Cardio-oncology service

- Primary prevention of cardiotoxicity in high-risk patients
- Secondary prevention of cardiotoxicity
- Management of other cardiovascular toxicity e.g. hypertension
- Pre-operative assessment for cancer surgery
- Investigation of suspected cardiac invasion by tumour

Classifying Cardiotoxicity Heart Failure

- Stage A: High-risk of heart failure, but ‘normal’ heart
- Stage B: Asymptomatic structural heart disease
- Stage C: Symptomatic structural heart disease
- Stage D: Refractory heart failure

Troponin I is valuable in detecting cardiotoxicity

- Increase in troponin
- Decrease in LVEF
- HF symptoms
- Detection of pre-clinical cardiotoxicity and prevention of UOF
- LVSD treatment and prevention of HF
- Treatment of symptomatic HF

Strategy for risk assessment and monitoring

<table>
<thead>
<tr>
<th>Table 2 Risk assessment and monitoring associated with left ventricular dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-related risk factors</td>
</tr>
<tr>
<td>Early cardio toxicity</td>
</tr>
<tr>
<td>Elevated LVEF (&lt;55%)</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
</tr>
<tr>
<td>Echocardiography</td>
</tr>
<tr>
<td>Baseline characteristics</td>
</tr>
<tr>
<td>Risk score (range)</td>
</tr>
<tr>
<td>Low risk score (&lt;55%)</td>
</tr>
<tr>
<td>Intermediate risk score (50%)</td>
</tr>
<tr>
<td>High risk score (&gt;50%)</td>
</tr>
</tbody>
</table>

Cardinale et al. Circ. 2004;109:2749-2754
BNP may also be an effective marker of subsequent myocardial damage


Imaging evaluation

- MUGA scans are inadequate and tell the story too late.
- 2D echo with Doppler imaging including evaluation of diastolic function should be the minimum.
- Increasing evidence that assessment of global left ventricular strain and twist provides significant information early when we can change the course.
- Strain imaging is not uniformly done at all centers.

The process is underway before the LVEF drops

Thavendiranathan et al, JACC, 2014.

Incremental prognostic factors for future anthracycline induced cardiotoxicity


Treatment Strategies

OVERCOME: Enalapril and carvedilol to prevent LVSD in malignant hemopathies

**OVERCOME: Enalapril and carvedilol to prevent LVSD in malignant hemopathies**

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>Enalapril</th>
<th>Carvedilol</th>
<th>Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of patients with LVSD (%)</td>
<td>2 (6.7)</td>
<td>4 (12.1)</td>
<td>6 (18.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Total mortality (%)</td>
<td>3 (9.5)</td>
<td>5 (15.1)</td>
<td>9 (27.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Death or heart failure (%)</td>
<td>3 (9.5)</td>
<td>5 (15.1)</td>
<td>10 (30.3)</td>
<td>0.009</td>
</tr>
<tr>
<td>Death, heart failure or repeat LVEF &lt; 40%</td>
<td>3 (9.5)</td>
<td>12 (36.4)</td>
<td>22 (66.7)</td>
<td>0.009</td>
</tr>
<tr>
<td>&gt;15% decrease in LVEF with a 5% LVEF &lt; 50%</td>
<td>2 (6.2)</td>
<td>4 (12.1)</td>
<td>8 (24.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Heart failure or &gt;30% decrease in LVEF (%)</td>
<td>4 (12.1)</td>
<td>7 (21.2)</td>
<td>18 (54.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>Serious adverse event (%)</td>
<td>9 (27.3)</td>
<td>13 (39.4)</td>
<td>15 (45.5)</td>
<td>0.15</td>
</tr>
</tbody>
</table>


**Carvedilol appears protective during adriamycin based chemotherapy**

![Graph showing EF% for Carvedilol and Control groups](image)

Kalay et al. JACC. Dec 2006. 48:2258-2262

**Evidence for significant reversibility of LV dysfunction with trastuzumab-related cardiac toxicity**


**Recovery of LV dysfunction with standard HF therapy**


**My patients..**

- SK is living at home with her LVAD, recovering well from her prolonged hospitalization/illness. She does not tolerate much neurohormonal modulation but her biventricular function is improved on LVAD with normal end organ function. Plan is to complete one year of maintenance therapy with ATRA and list for OHT.

- RC is continuing treatment which has included pertuzumab and trastuzumab. She has not had symptoms and is currently on ACE and BBL therapy with stable LV function. She is on anticoagulation for PE. Statin therapy was recommended for nonobstructive mild CAD given her risk factors. This will be started once her current chemo finishes per oncology request.
Cancer and cardiovascular disease are by far the most common disease conditions in the developed world and they often co-exist. When considering cardiovascular disease in the setting of cancer treatment, it may pre-exist or it may be caused by it—the goal is to treat the cancer and optimize long term cardiovascular health. Use of biomarkers and advanced imaging can allow for earlier detection of cardiovascular compromise during oncologic treatment and permit aggressive treatment of both cancer and heart disease. Use of a coordinated team and treatment approach is needed to ensure consistent care for a complex patient population.