Cardio-Oncology: Detection and Treatment of Chemotherapy-Induced Cardiac Dysfunction

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Epidemiology of Heart Disease in Cancer Patients
Heart disease and cancer remained the 1st and 2nd leading causes of death, respectively, over the 75-year period.

Figure 2. Percentage of all deaths due to five leading causes of death by year: United States, 1935–2010

NOTE: 2010 data are preliminary.
Deaths due to Heart Disease and Cancer

NOTES: Leading cause is based on number of deaths. Access data table for Figure 1 at: http://www.cdc.gov/nchs/data/databriefs/db254_table.pdf#1.

Heart disease patients are more likely to have a higher risk of cancer than the general population.
Interactions between Heart Disease, Risk Factors, Cancer, Cancer Therapy

Shared Risk Factors:
- Smoking
- Obesity
- Nonprudent Diet
- Physical Inactivity

\(\uparrow\) Cancer Risk

CANCER

- Radiation
- Targeted Therapy

\(\uparrow\) Cardiac Risk

Cancer Survivors:
- Less therapy offered because of CVD
- Cardiotoxicity limits therapy

High Long-Term Risk

\(\uparrow\) Cancer Risk:
- Cardiotoxic cancer therapy
- Worsening risk factors

Risk Factors Persist During Cancer Treatment
Risk Factors May Worsen During Cancer Treatment

Clinical Cardiovascular Disease at Cancer Diagnosis
Subclinical Cardiovascular Disease at Cancer Diagnosis

Perioperative Cardiac Events
Cardiotoxicity From Cancer Therapy
Many of these survivors have had radiation or chemotherapy, with potential long-term cardiovascular toxicities; attenuate clinical success of oncologic treatments.
Estimated Numbers of Cancer Survivors by State as of January 1, 2014
Heart Disease in Cancer: Risks

• > 50% of all patients exposed to chemotherapy will show some degree of cardiac dysfunction 10 to 20 years after chemotherapy
  – 5% will develop overt heart failure
  – 40% will experience arrhythmias
  – Eight-fold higher cardiovascular mortality when compared with the general population
Oncologic Treatments: Long-term Risk of HF, Despite Short-term Reassurance

Reducing cardiac reserve

Increasing risk of heart failure

Cardiac function (% of normal)

Age

Healthy
Cardiac risk factors
Cancer survivor
Survivors of Childhood Cancer: Cumulative Incidence by Organ Systems

- New Malignancy
- Hearing
- Renal
- Cardiac
- Vision
- Respiratory

Armstrong et al, ASCO 2012
Tukenova et al, JCO 2010
Chemotherapy and Heart Disease
Chemotherapy and the Heart: Why?

- Cardiac Cells do not divide
  - High protein synthesis
  - High metabolism
- Do not regenerate?
- Rely heavily on ordered cell-cell communication
- Responsive to biologic stress
- Consist of terminally differentiated cells unprotected by a vascular barrier
- Susceptible to permanent and adverse effects of chemo and radiation therapy
Chemotherapy-Induced Cardiovascular Toxicity

**Cardiomyopathy/Heart Failure**
- Antimetabolites (5-FU, capecitabine)
- Alkylating agents (cyclophosphamide, ifosfamide)
- Antimicrotubule agents (docetaxel)
- Monoclonal antibody (bevacizumab, trastuzumab)
- TKIs (dasatinib, imatinib, lapatinib, sunitinib)
- Antimetabolites (clofarabine)
- Proteasome inhibitors (bortezomib)

**Hypertension**
- Monoclonal antibody-based TKI (bevacizumab)
- Small molecule TKIs (sorafenib, sunitinib, pazopanib, axitinib, cediranib)
- VEGF trap: Afibercept

**Ischemia**
- Angiogenesis inhibitor (thalidomide)
- Antimicrotubule agent (paclitaxel)
- Histone deacetylase inhibitor (vorinostat)
- Small molecule TKIs (dasatinib, lapatinib, nilotinib)
- Miscellaneous (arsenic trioxide)

**Arrhythmias**
- (bradycardia, QT prolongation)
<table>
<thead>
<tr>
<th>Chemotherapy agents</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthracyclines (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>
</tr>
<tr>
<td>Clofarabine</td>
<td>27</td>
</tr>
<tr>
<td><strong>Antimicrotubule agents</strong></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>2.3–13</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Monoclonal antibodies</strong></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>1.7–20.1³ᵃᵇ</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1.6–4ᵃⁿ</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>
</tr>
<tr>
<td>Sunitinib</td>
<td>2.7–19</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>7–11</td>
</tr>
<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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<td>Lapatinib</td>
<td>0.2–1.5</td>
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<td>Nilorinib</td>
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<tr>
<td><strong>Proteasome inhibitors</strong></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>
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<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
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<tr>
<td>Everolimus</td>
<td>&lt;1</td>
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<tr>
<td>Temsirolimus</td>
<td>&lt;1</td>
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</tbody>
</table>
Doxorubicin: Uses

• Treatment of *acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin’s disease, Breast cancer, malignant lymphoma, soft tissue and bone sarcomas, thyroid cancer, small cell lung cancer, gastric cancer, ovarian cancer, bladder cancer, neuroblastoma, and Wilms' tumor*

• Unlabeled Treatment of multiple myeloma, endometrial carcinoma, uterine sarcoma, head and neck cancer, liver cancer, kidney cancer
Mechanism of Anthracycline-Induced Cardiotoxicity

Harake et al, Future Cardiol. 2012
Vacuolization with Reduced Ejection Fraction due to Anthracycline Cardiotoxicity

Lightfoot et al, Circ. Cardiovasc. Imag. 2010
## Risk Factors for Anthracycline-Induced Cardiotoxicity

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative anthracycline dose</td>
<td>Cumulative doses &gt;500 mg/m² associated with marked long-term risk</td>
</tr>
<tr>
<td>Length of post-therapy interval</td>
<td>Incidence of clinically important cardiotoxicity increases progressively after therapy</td>
</tr>
<tr>
<td>Rate of anthracycline administration</td>
<td>Prolonged administration to minimize circulating dose volume may decrease toxicity; results are mixed</td>
</tr>
<tr>
<td>Individual anthracycline dose</td>
<td>Higher individual anthracycline doses are associated with increased late cardiotoxicity, even when cumulative doses are limited</td>
</tr>
<tr>
<td>Type of anthracycline</td>
<td>Liposomal encapsulated preparations may reduce cardiotoxicity. Data detailing anthracycline analogs and cardiotoxicity differences are conflicting</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>Cumulative radiation dose &gt;30 Gy; prior or concomitant anthracycline treatment</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td>Trastuzumab, cyclophosphamide, bleomycin, vincristine, amscarine and mitoxantrone, among others, may increase susceptibility or toxicity</td>
</tr>
<tr>
<td>Pre-existing cardiac risk factors</td>
<td>Hypertension; ischemic, myocardial and valvular heart disease; prior cardiotoxic treatment</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Diabetes, obesity, renal dysfunction, pulmonary disease, endocrinopathies, electrolyte and metabolic abnormalities, sepsis, infection, pregnancy</td>
</tr>
<tr>
<td>Age</td>
<td>Both young and advanced age at treatment are associated with increased risk</td>
</tr>
<tr>
<td>Sex</td>
<td>Females are at greater risk than males</td>
</tr>
<tr>
<td>Additional factors</td>
<td>Trisomy 21; African–American ancestry</td>
</tr>
</tbody>
</table>
**Trastuzumab: Uses**

- **Breast cancer, adjuvant treatment, HER2+**
  - Following completion of anthracycline-based chemotherapy
  - With concurrent paclitaxel or docetaxel
  - With concurrent docetaxel/carboplatin

- **Breast cancer, metastatic, HER2+**
  - Either as a single agent or in combination with paclitaxel

- **Gastric cancer, metastatic, HER2+**
  - In combination with cisplatin and either capecitabine or fluorouracil for 6 cycles followed by trastuzumab monotherapy

- **Breast cancer, metastatic, HER2+ (unlabeled combinations)**
Trastuzumab: Mechanism of Action

- **Trastuzumab** binds to HER2 receptors on cancer cells, leading to signaling disruption.

- EGFR and HER2 receptors are shown on the cell surface.

- The binding of Trastuzumab to HER2 inhibits downstream signaling pathways, stopping the growth of HER2+ tumor cells.

- NK cells are activated to mediate cytotoxicity against the tumor cells.

Adapted from LOUIS M. WEINER, MD
Cumulative Incidence of Heart Failure: Anthracycline vs. Trastuzumab

Total N: 12,500
- AC: 3697
- TZ: 112
- AC + TZ: 442
- Other: 2442
- None: 5807
Mean age: 60y

<table>
<thead>
<tr>
<th>Cumulative Incidence (95% CI), %</th>
<th>Anthracyline only</th>
<th>Trastuzumab only</th>
<th>Anthracyline + Trastuzumab</th>
<th>Other chemotherapy</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.2 (1.0 to 1.5)</td>
<td>2.0 (1.6 to 2.4)</td>
<td>2.7 (2.2 to 3.2)</td>
<td>3.5 (2.8 to 4.1)</td>
<td>4.3 (3.5 to 5.0)</td>
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<tr>
<td></td>
<td>3.6 (1.5 to 5.6)</td>
<td>5.8 (2.5 to 8.9)</td>
<td>7.8 (3.4 to 12.0)</td>
<td>9.9 (4.3 to 15.1)</td>
<td>12.1 (5.3 to 18.3)</td>
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<tr>
<td></td>
<td>6.2 (4.1 to 8.2)</td>
<td>9.8 (6.7 to 12.8)</td>
<td>13.2 (9.1 to 17.1)</td>
<td>16.5 (11.5 to 21.3)</td>
<td>20.1 (14.0 to 25.6)</td>
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<tr>
<td></td>
<td>1.3 (1.0 to 1.6)</td>
<td>2.1 (1.7 to 2.5)</td>
<td>2.9 (2.4 to 3.4)</td>
<td>3.7 (3.0 to 4.3)</td>
<td>4.5 (3.7 to 5.3)</td>
</tr>
<tr>
<td></td>
<td>0.9 (0.7 to 1.0)</td>
<td>1.4 (1.2 to 1.7)</td>
<td>1.9 (1.6 to 2.3)</td>
<td>2.5 (2.1 to 2.9)</td>
<td>3.1 (2.6 to 3.5)</td>
</tr>
</tbody>
</table>

Bowles et al, J Natl Cancer Inst 2012
### Potential risk factors for the development of trastuzumab-associated cardiac dysfunction

<table>
<thead>
<tr>
<th>Cardiovascular factors</th>
<th>Noncardiovascular factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular dysfunction</td>
<td>Doxorubicin exposure</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Older age</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>Chest wall irradiation (especially to the left side)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>Obesity</td>
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</tbody>
</table>
Anti-Angiogenic Inhibitors for Cancer Treatment

- Metastatic colorectal cancer, advanced non-small cell lung cancer, renal cell carcinoma, glioblastoma, hepatocellular carcinoma, GI stromal tumors, pancreatic cancer, neuroendocrine tumors, soft tissue sarcoma, medullary thyroid cancer
- CML (Imatinib)
  - Developed in the 1990s, it was the first approved kinase inhibitor (in 2001), a revolutionary success for the treatment of CML, and a major step towards targeted therapy
FDA-Approved Anti-Angiogenic Inhibitors for Cancer Treatment

Moslehi, Circ. 2015
Targeted Therapies: VEGF and VEGF-Associated Receptors & Ligands, and Specific Drug Therapies

Mohananey, Kumar, Okwuosa. Cardiovascular Toxicity of Anti-Angiogenic Therapy: Mechanism and Management, 2016
VSP Inhibitors: Mechanism of Action and Effects

- Hypertension
- Cardiomyopathy
- Arterial thrombosis
- QT Prolongation
-- Edema
<table>
<thead>
<tr>
<th>Class</th>
<th>Anti-Angiogenic Agent (Trade Names)</th>
<th>Major Cardiovascular Adverse Events</th>
</tr>
</thead>
</table>
| Monoclonal Antibodies*                    | Bevacizumab (Avastin®) Cetuximab (Erbitux®) Panitumumab (Vectibix®) | • Hypertension (56%; grades 3/4: 19%)*  
  • ATEs: stroke, MI, TIA, angina, and other ATEs (~ 6%)  
  • VTEs (~ 12%)  
  • Proteinuria (up to 38%)  
  • Peripheral edema  
  • Cardiomyopathy with systolic LV dysfunction (~ 4%) |
| Recombinant Monoclonal Antibody           | Ramucirumab (Cyramza®) Necitumumab (Portrazza®)           | • Hypertension (ram: 16%; grades 3/4: 8%)  
  • ATEs: MI, cardiac arrest, CVA, and cerebral ischemia (ram: 2%; nec: 5%)  
  • Proteinuria (ram: 29.7%)  
  • VTE (nec: 9%; grades 3/4: 5%) |
| VEGF Decoy Receptor (VEGF trap)           | Aflibercept (Zaltrap®)                                     | • Hypertension (41%; grades 3/4: 19%)  
  • Proteinuria (62%; grades 3/4: 8%)  
  • Creatinine increased (23%)  
  • VTEs (9%)  
  • ATEs (3%; grades 3/4: 2%) |
| Small Molecule TKIs†                      | Gefitinib (Iressa®) Erlotinib (Tarceva®) Sorafenib (Nexavar®)‡ Sunitinib (Sutent®) Lapatinib (Tykerb®) Pazopanib (Votrient®) Vandetanib (Caprelsa®) Axitinib (Inlyta®) Regorafenib (Stivarga®) Cabozanitinib (Cometiq®) Nintedanib (Ofev®) Lenvatinib (Lenvima®) | • Hypertension (9-72%; grades 3/4: 2-33%)  
  • ATEs (1-11%; grades 3/4: 1-8%)  
  • VTEs (1-14%; grades 3/4: 3-9%)  
  • Cardiomyopathy/heart failure (4.7 – 28%)  
  • QTc prolongation#  
  • Proteinuria (2.3-36%; all grades) |

Mohananey, Kumar, Okwuosa.  
Cardiovascular Toxicity of Anti-Angiogenic Therapy: Mechanism and Management, 2016
Diagnosis of Cardiotoxicity Associated with Chemotherapy
Stages in Heart Failure Development/Recommended Therapy by Stage

**At Risk for Heart Failure**

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF

*E.g., Patients with:*
- HTN
- Atherosclerotic disease
- DM
- Obesity
- Metabolic syndrome or
- Using cardiotonics
- With family history of cardiomyopathy

**THERAPY**
- Goals: Heart healthy lifestyle
- Prevent vascular, coronary disease
- Do not prevent LV structural abnormalities
- Drugs: ACEI or ARB in appropriate patients for vascular disease or DM
  - Statins as appropriate

**STAGE B**
Structural heart disease but without signs or symptoms of HF

*E.g., Patients with:*
- Previous MI
- LV remodeling including LHV and low EF
- Asymptomatic valvular disease

**THERAPY**
- Goals: Prevent HF symptoms
- Prevent further cardiac remodeling
- Drugs: ACEI or ARB as appropriate
- Beta blockers as appropriate
  - In selected patients:
    - ICD
    - Revascularization or valvular surgery as appropriate

**STAGE C**
Structural heart disease with prior or current symptoms of HF

*E.g., Patients with:*
- Known structural heart disease and
- HF signs and symptoms

**THERAPY**
- Goals: Control symptoms
- Improve HRQOL
- Prevent hospitalization
- Reduce mortality
- Drugs for routine use:
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
- Drugs for use in selected patients:
  - Hydralazine/isosorbide dinitrate
  - ACEI and ARB
  - Digoxins
  - In selected patients:
    - CRT
    - ICD
    - Revascularization or valvular surgery as appropriate

**STAGE D**
Refactory HF

*E.g., Patients with:*
- Marked HF symptoms at rest
- Recurrent hospitalizations or death GDMT

**THERAPY**
- Goals: Control symptoms
- Improve HRQOL
- Reduce hospital readmissions
- Establish patient's end-of-life goals
- Options:
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation
Strain and Troponin-I for Prediction of Cardiotoxicity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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</thead>
<tbody>
<tr>
<td>10% decrease long strain</td>
<td>7/9 (78%)</td>
<td>27/34 (79%)</td>
<td>7/14 (50%)</td>
<td>27/29 (93%)</td>
</tr>
<tr>
<td>Increased cTnl at 3 months</td>
<td>6/9 (67%)</td>
<td>28/34 (82%)</td>
<td>6/12 (50%)</td>
<td>28/31 (90%)</td>
</tr>
<tr>
<td>10% decrease long strain and increased cTnl at 3 months</td>
<td>5/9 (55%)</td>
<td>33/34 (97%)</td>
<td>5/6 (83%)</td>
<td>33/37 (89%)</td>
</tr>
<tr>
<td>10% decrease long strain or increased cTnl at 3 months</td>
<td>8/9 (89%)</td>
<td>22/34 (65%)</td>
<td>8/20 (40%)</td>
<td>22/23 (97%)</td>
</tr>
</tbody>
</table>

Testing Based on Pathophysiology

Patho-physiology

Exposure
- Disrupted mitochondrial function & actin-myosin interaction
- Intra- and extracellular edema, inflammation, cell injury
- Impaired regional LV function
- Myocardial death, collagen deposition, LV remodelling
- Decreased LVEF, cardiac output
- Neurohormonal activation, CHF

Echo vs. MUGA

Surveillance
- + MRI contrast signal intensity
- MRI T2 signal
- + serum cardiac Troponin I
- Abnormal regional function
- + serum BNP measurement
- Decreased LVEF
- Exercise capacity

Blood Work

Strain Imaging

Adapted from Hundley 2012
### Markers Associated with Cardiotoxicity in Breast Cancer Patients, and Strength of Evidence

<table>
<thead>
<tr>
<th>Markers</th>
<th>Strength of Evidence on Radiotherapy†</th>
<th>Strength of Evidence on Chemotherapy#</th>
<th>Strength of Evidence Overall‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS≠</td>
<td>++++ (5)</td>
<td>+++ (6)</td>
<td>++++</td>
</tr>
<tr>
<td>Troponin-I*</td>
<td>+++ (5)</td>
<td>+++ (20)</td>
<td>+++</td>
</tr>
<tr>
<td>Troponin-T*</td>
<td>++ (3)</td>
<td>+++ (18)</td>
<td>+++</td>
</tr>
<tr>
<td>BNP*</td>
<td>++++ (5)</td>
<td>+++ (8)</td>
<td>++++</td>
</tr>
<tr>
<td>NT-pro-BNP*</td>
<td>+++ (3)</td>
<td>++++ (25)</td>
<td>+++</td>
</tr>
</tbody>
</table>

*Silver, Palomo, Okwuosa. Identification of At-Risk Patients and Comorbidities that Increase Risk, 2016*
• 58-year-old African American woman with history of inflammatory breast cancer, which is triple negative, currently stage IV with metastases to the bone marrow.

• Status post Adriamycin, cyclophosphamide dosing for a total of 11 cycles initially at a reduced dose and then at a higher dose, total Adriamycin dose now of approximately 540 mg/sq m.

• After 300mg/sq m, followed with serial echos, strain, troponin and BNP
Baseline Echo Strain

Feigenbaum et al, Circulation J. 2012
Echo Strain with Chemotherapy

Peak Systolic Strain

HR = 105 bpm
AP2 L. Strain = -8 %
AP4 L. Strain = -9 %
AP3 L. Strain = -11 %
G.L. Strain (Avg.) = -9 %
Patient PM

- Trop increased to 0.236
- BNP increased to 539
- Strain became abnormal, EF 56% by echo with contrast
  - Could not change HF meds dose due to hypotension, and patient resistance
- Next cycle: EF 47%; trop and BNP about the same
The Case of AF, 6651823

- 41 year old female with history of STAGE IIIA non-Hodgkin lymphoma, diagnosed about 20 years prior s/p chemotherapy but no radiation therapy, now with new diagnosis of anaplastic large cell lymphoma requiring treatment with possibly doxorubicin based regimen
- She presented to our cardio-oncology clinic to establish care as she would be going for chemotherapy involving doxorubicin again
- S/p CHOP with ~ 300 mg/m2 of doxorubicin
- Planned for same therapy a second time
AF Pre-Chemo Strain (Ap 3)
AF Pre-Chemo Strain (Ap 2)
AF Pre-Chemo Strain (Ap 3)
HR = 88 bpm
AP2 L. Strain = -20%
AP4 L. Strain = -19%
AP3 L. Strain = -18%
G.L. Strain (Avg.) = -19%

Peak Systolic Strain
AF Intra-Chemo Strain - after 2 cycles (Ap 3)
AF Intra-Chemo Strain - after 2 cycles (Ap 2)
AF Intra-Chemo Strain - after 2 cycles (Ap 4)
HR = 71 bpm
AP2 L. Strain = -17%
AP4 L. Strain = -17%
AP3 L. Strain = -15%
G.L. Strain (Avg.) = -17%
AF Strain 1 Year Later - Ap 3
AF Strain 1 Year Later - Ap 2
AF Strain 1 Year Later - Ap 4
HR = 69 bpm
AP2 L. Strain = -18%
AP4 L. Strain = -16%
AP3 L. Strain = -14%
G.L. Strain (Avg.) = -16%
29 year old Caucasian male with history of rhabdomyosarcoma to multiple bony areas, s/p chemotherapy and radiation therapy

Presents with diagnosis of HFrEF on most recent echocardiogram; left ventricular ejection fraction of ~38%

Thought to be related to his chemotherapy which included a doxorubicin
RD, HPI

- Complains of shortness of breath which he states began a few months prior. Dyspnea on exertion - a little - with climbing up a flight of stairs. He has some fatigue which he says is more his difficulty, rather than shortness of breath. No orthopnea or PND. Some dizziness with standing (orthostatic dizziness). Now he gets up slowly - happens more with treatments. Apparently, recently he has not been thinking as clearly as he used to.
• He returned from Mexico a month prior (he was there for about 5 days), but states his shortness of breath began before that. In Mexico, he had chills, diarrhea, no fevers. Went to emergency room in Mexico. He was given antibiotics in Mexico. This resolved within a day. He then had a blood pressure of about 70s/40s while in Mexico, which normalized about 3 days later when they returned to the US. Face became puffy after he came back to the US. Subsided since after antibiotics was stopped.
RD, Oncology Treatment

- S/p chemotherapy with multiple drugs on the ARST0431 Rhabdomyosarcoma protocol, including doxorubicin (under 240mg/m2), irinotecan, vincristine, etoposide, ifosfamide, cyclophosphamide, dactinomycin...

- S/p radiation therapy to L2 and L3 from Nov. 5 - Nov. 16 2012; and to right femur, pelvic bone and clavicle, and to left scapula and inguinal region from May - June 2013
RD, Initial Echo Strain Bull’s Eye
Labs

TSH  157.863   Range: 0.350 - 4.940 uIU/ML
FREE THYROXINE  <0.4   Range: 0.7 - 1.5  NG/DL
FREE T3   1.0   Range: 1.7 - 3.7 PG/ML
Labs explained his issues

• Very high TSH of ~158. This could explain a lot of his issues including cardiomyopathy, pericardial effusion, fatigue, neurological symptoms, and maybe even his elevated creatinine.

• Very low index of suspicion for chemotherapy-induced cardiomyopathy → chemo dose
RD, 4 Months Post Thyroid Replacement Therapy
Treatment/Prevention of Cardiotoxicity Associated with Chemotherapy
Changes in LV Ejection Fraction after Heart Failure Therapy (ACE-I/BB)

Cardinale et al, JACC 2010
Recovery of LV Systolic Function is Dependent on Time to Heart Failure Treatment

Percentage of Responders According to the Time Elapsed From AC Administration to Start of Heart Failure Therapy

Cardinale et al, JACC 2010
ACE-Is/ARBs for Prevention of Chemotherapy-Induced Cardiotoxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Cohort</th>
<th>Flu time</th>
<th>Cardiotoxic chemotherapy</th>
<th>Radiation therapy</th>
<th>Preventive therapy</th>
<th>Cardiotoxicity definition</th>
<th>Outcome with vs without previous therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silber et al (AAA study), 2004</td>
<td>2004</td>
<td>Pediatric cancer survivors with ≥1 cardiac abnormalities in flu (n=135)</td>
<td>35 mo</td>
<td>Anthracyclines 300 mg/m²</td>
<td>36% Enalapril 0.05-0.15 mg/kg per d</td>
<td>FS (%)</td>
<td>LVESWS (g/cm²)</td>
<td>Interaction term (change due to treatment) P=.84</td>
</tr>
<tr>
<td>Cardinale et al, 2006</td>
<td>2006</td>
<td>HDC (n=114, 60% NHL and breast cancer) &amp; cTnl &gt;ULN within 3 d of any cycle</td>
<td>12 mo</td>
<td>Various, cumulative doxorubicin equivalent dose 335 mg/m²</td>
<td>11% Enalapril 2-20 mg/d, administered after cTnl elevation and continued in flu</td>
<td>LVEF decrease &gt;10% to &lt;50%, rate (%)</td>
<td>HF rate (%)</td>
<td>Interaction term (change due to treatment) P=.28</td>
</tr>
<tr>
<td>Nakamme et al, 2005</td>
<td>2005</td>
<td>NHL (n=40)</td>
<td>Day 3 after CHOP initiation</td>
<td></td>
<td>0% Valsartan 80 mg/d, administered and continued with CT</td>
<td>LVEDD (mm)</td>
<td>BNP (pmoVL)</td>
<td>45 vs 49b</td>
</tr>
<tr>
<td>Dessi et al, 2011</td>
<td>2011</td>
<td>Various (n=49, breast cancer 37%)</td>
<td>12 mo</td>
<td>Epirubicin 400 mg/m²</td>
<td>0% Telmisartan 40 mg/d, administered</td>
<td>Strain rate</td>
<td>QTc interval (ms)</td>
<td>420 vs 435b</td>
</tr>
</tbody>
</table>

# Beta Blockers for Prevention of Chemotherapy-Induced Cardiotoxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Cohort</th>
<th>F/u time</th>
<th>Cardiotoxic chemotherapy</th>
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<th>Cardiotoxicity definition</th>
<th>Outcome with vs without previous therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seicean et al.</td>
<td>2013</td>
<td>Breast cancer (n=318)</td>
<td>3±2 y</td>
<td>Anthracyclines and/or Herceptin</td>
<td>59%</td>
<td>Any BB therapy during CT</td>
<td>Rate of new HF admission (%)</td>
<td>4.7 vs 12.7 (HR, 0.2; 95% CI, 0.1-0.7)</td>
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<tr>
<td>Randomized controlled trials</td>
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<tr>
<td>Kalay et al.</td>
<td>2006</td>
<td>Breast cancer (68%), 6 mo lymphoma (18%)</td>
<td>1 wk after CT</td>
<td>Anthracyclines: doxorubicin 520 mg/m² or epirubicin 780 mg/m²</td>
<td>0%</td>
<td>Carvedilol 12.5 mg/d, administered before CT and continued for 6 mo</td>
<td>LVEF (%)</td>
<td>Carvedilol no change; Control significant decrease (68.9-52.3)</td>
</tr>
<tr>
<td>El-Shitany et al.</td>
<td>2012</td>
<td>Children with ALL (n=50)</td>
<td>1 wk after CT</td>
<td>Doxorubicin 120 mg/m²</td>
<td>0%</td>
<td>Carvedilol 0.1-1 mg/d, administered 5 d before CT and continued for 6 mo</td>
<td>FS (%)</td>
<td>39.5±6.3 vs 33.5±6.2 (HR, 0.2; 95% CI, 0.1-0.7)</td>
</tr>
<tr>
<td>Elitok et al.</td>
<td>2013</td>
<td>Breast cancer (n=80)</td>
<td>6 mo</td>
<td>Anthracyclines 520 mg/m²</td>
<td>0%</td>
<td>Carvedilol 12.5 mg/d, administered before CT and continued for 6 mo</td>
<td>GPSS (%)</td>
<td>−19.3±2.0 vs −15.1±1.8 (HR, 0.2; 95% CI, 0.1-0.7)</td>
</tr>
<tr>
<td>Kaya et al.</td>
<td>2012</td>
<td>Breast cancer (n=45)</td>
<td>6 mo</td>
<td>Anthracyclines: doxorubicin 246 mg/m² or epirubicin 354 mg/m²</td>
<td>27%</td>
<td>Nebivolol 5 mg/d, administered 7 d before CT and continued for 6 mo</td>
<td>Peak systolic strain, septal (%)</td>
<td>20±5.3 vs 16±4.3 (HR, 0.2; 95% CI, 0.1-0.7)</td>
</tr>
<tr>
<td>Georgakopoulos et al.</td>
<td>2010</td>
<td>HL and NHL (n=125)</td>
<td>12 mo</td>
<td>ABVD</td>
<td>21%</td>
<td>Metoprolol 25-50 mg BID or enalapril 2.5-10 mg BID, administered with CT</td>
<td>LVEF (%)</td>
<td>64±5.1 vs 63±4.8 (HR, 0.2; 95% CI, 0.1-0.7)</td>
</tr>
<tr>
<td>Bosch et al. (OVERCOME trial)</td>
<td>2013</td>
<td>Acute leukemia (n=36) or HSCT (n=54)</td>
<td>6 mo</td>
<td>Anthracyclines (40% before, 40% during, cumulative 265 mg/m²)</td>
<td>18%</td>
<td>Carvedilol (6.25-25 mg BID) and enalapril (2.5-10 mg BID), administered 24 h before CT and continued in f/u</td>
<td>New HF rate (%)</td>
<td>2.4 or 4.7 vs 0 (P=.56)</td>
</tr>
</tbody>
</table>

Statins for Prevention of Chemotherapy-Induced Cardiotoxicity

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<tr>
<td>Observational studies</td>
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<tr>
<td>Seicean et al, 2012</td>
<td>2012</td>
<td>Breast cancer (n=628)</td>
<td>2.6±1.7 y</td>
<td>Anthracyclines</td>
<td>66%</td>
<td>Any statin therapy during CT</td>
<td>Rate of new HF admission (%)</td>
<td>6.0 vs 17.2&lt;sup&gt;b&lt;/sup&gt; (HR, 0.3; 95% CI, 0.1-0.9)</td>
</tr>
<tr>
<td>Acar et al, 2011</td>
<td>2011</td>
<td>Various (n=40)</td>
<td>6 mo</td>
<td>Anthracyclines; doxorubicin 256 mg/m²; idarubicin 297 mg/m²</td>
<td>NA</td>
<td>Atorvastatin 40 mg/d, administered before and continued for 6 mo after CT</td>
<td>LVEF (%), absolute change</td>
<td>1.3 vs -7.9&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>LVEDD (mm), absolute change</td>
<td>-0.15 vs 2.0&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td>LVESD (mm), absolute change</td>
<td>-1.35 vs 2.1&lt;sup&gt;b&lt;/sup&gt;</td>
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</tr>
</tbody>
</table>
Statin Use in Cancer Patients: Danish Registry

N = 295,475
18,271 statin
277,204 no statin
≥ 40 yrs with cancer diagnosis

Nielsen et al, NEJM 2012
Dexrazoxane for Preventing Doxorubicin-Induced Cardiotoxicity

Harake et al, Future Cardiol. 2012
Examples of major mechanisms causing cardiotoxicity of anticancer treatments, clinically used therapeutic agents, and potential protective agents.
Cardio-Oncology Program: Cardiovascular Disease in Cancer Patients

GOALS: TEAMWORK COLLABORATION IMPROVE OUTCOMES DEVELOP GUIDELINES

Cardiology

Nurses

Oncology

Rehabilitation Services

Social Worker

Nutritionist

Pharmacist

Case Manager

Patient/Family
“The aim of Cardio Oncology is NOT to prevent cancer patients with cardiovascular disease and risk factors from receiving necessary life-saving cancer therapy, but to prevent and/or treat cardiac disease as best as possible ALONGSIDE their cancer therapy/care.”

Tochi M. Okwuosa
Questions?