Cardiovascular Complications of Cancer Therapy: The Emerging Field of Cardio-Oncology

Michael Fradley, MD
Current Perspectives in Oncology Nursing
February 16, 2017
Disclosures:

- Ariad Pharmaceutics – Advisory Board
Objectives

- Discuss frequently encountered cardiovascular complications in cancer patients and survivors
- Highlight cancer therapies with associated cardiotoxicity
- Identify novel diagnostic and treatment strategies for cardiotoxicities
Scope Of The Problem

- 1 of 3 adults have CV disease (82 million)
- 12 million cancer patients; 12 million cancer survivors
- Approximately 30% of patients receiving cancer therapy will have cardiovascular complications
- Some complications may not become apparent for 10-20 years after completion of treatments
Trends in 5-Year Cancer Survival

5-year survival by tumour type 1971 vs 2011 (predicted)
Progression of CV Complications in Cancer Patients

CV Disease: Common after Cancer Treatment

Chun Chao et al. JCO 2016;34:1626-1633
CV Disease: Common after Cancer Treatment

- A. Coronary Artery Disease
- B. Valve Disease
- C. Arrhythmias
- D. Heart Failure

Gregory T. Armstrong et al. JCO 2013;31:3673-3680
CV Disease: Common after Cancer Treatment

A. Hypertension
B. Dyslipidemia
C. Diabetes
D. Obesity
E. Multiple Cardiac RF

Gregory T. Armstrong et al. JCO 2013;31:3673-3680
Cardio-Oncology: Definition

- Cardio-oncology is a multidisciplinary field aimed at managing cardiovascular risk and preventing cardiovascular disease in cancer patients and survivors.

- Eliminate cardiac disease as a barrier to effective cancer therapy
Cardio-Oncology – A Collaborative Discipline

Sliding Doors Concept

65 year old Female Smoker with Shortness of Breath
Oncologist

Breast Cancer Identified

Surgery and Adriamycin-based chemotheraphy

Cancer Remission with Adriamycin-induced Heart Failure

Cardio-Oncologist Prevents both metastases and heart failure

Cardio-Oncologist

Ischemic Heart Disease Identified

Medical Therapy and Revascularization

Stable CV status; lung cancer with brain metastases

Adapted from Alini et al. JNCI. 2010.
Cardiomyopathy and Heart Failure
# Chemotherapy Induced LV Dysfunction

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Incidence (%)</th>
<th>Frequency of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthracycline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Doxorubicin (Adriamycin)</td>
<td>3-26</td>
<td>+++</td>
</tr>
<tr>
<td>• Epirubicin</td>
<td>0.9-3.3</td>
<td>++</td>
</tr>
<tr>
<td>• Idarubicin</td>
<td>5-18</td>
<td>+</td>
</tr>
<tr>
<td><strong>Alkylating Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cyclophosphamide (Cytoxan)</td>
<td>7-28</td>
<td>+++</td>
</tr>
<tr>
<td>• Ifosfamide</td>
<td>17</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Antimetabolites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clofarabine</td>
<td>27</td>
<td>+</td>
</tr>
<tr>
<td><strong>Antimicrotubule Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Docetaxel (Taxotere)</td>
<td>2.3-8</td>
<td>++</td>
</tr>
<tr>
<td><strong>Monoclonal Antibody Inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bevacizumab (Avastin)</td>
<td>1.7-3</td>
<td>++</td>
</tr>
<tr>
<td>• Trastuzumab (Herceptin)</td>
<td>2-28</td>
<td>++</td>
</tr>
<tr>
<td><strong>Proteasome Inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bortezomib</td>
<td>2-5</td>
<td>++</td>
</tr>
<tr>
<td>• Carfilzomib</td>
<td>11-25</td>
<td>+</td>
</tr>
<tr>
<td><strong>Small Molecule Tyrosine Kinase Inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dasatinib</td>
<td>2-4</td>
<td>++</td>
</tr>
<tr>
<td>• Sunitinib</td>
<td>2.7-11</td>
<td>+</td>
</tr>
</tbody>
</table>

Cardiotoxicity – Definitions

- Decline in initial EF by more than 10% to less 53% regardless of CHF symptoms

Type 1 Cardiotoxicity
- Structural and cellular changes (vacuolization, myofibrillar disarray)
- Cellular necrosis
- Irreversible

Type 2 Cardiotoxicity
- No structural or cellular changes
- Signaling abnormalities lead to cardiac stress
- Reversible

Decline in initial EF by more than 10% to less than 53% regardless of CHF symptoms
Anthracycline Induced Cardiomyopathy

Anthracycline Induced Cardiomyopathy

Anthracycline Induced Cardiomyopathy

Anthracycline Induced Cardiomyopathy: Risk Factors

- Cumulative Dose
- Age
- Female Gender
- Concomitant use of additional chemotherapy or XRT
- Underlying CV disease
LV Dysfunction and Targeted Therapies

- HER2+ Targeted Therapies
  - Trastuzumab (Herceptin)
  - Pertuzumab (Perjeta)

- Sunitinib
Trastuzumab and LVEF

Slamon, NEJM, 2011
Significant Heart Failure Associated with Trastuzumab

Ewer and Ewer, Nat. Rev Cardiovasc Med, 2010
Mechanism of Trastuzumab Cardiotoxicity

Hansel, Nat Rev Drug Discov, 2010
Trastuzumab Cardiac Monitoring Algorithm

Trastuzumab Cardiotoxicity Increases Over Time

Trastuzumab and Anthracycline Cardiotoxicity: Fibrosis and Apoptosis

TKI Induced LV Dysfunction

## Risk of CHF with Sunitinib

### Table: Risk of CHF with Sunitinib

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib</th>
<th>Control</th>
<th>Relative Risk</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demetri (2006)</td>
<td>22/202 10.9 (7.3 to 16.0)</td>
<td>3/102 2.9 (1.0 to 8.7)</td>
<td>3.70 (1.14 to 12.1)</td>
<td>.03</td>
</tr>
<tr>
<td>Motzer (2009)</td>
<td>78/375 20.8 (17.0 to 25.2)</td>
<td>44/360 12.2 (9.2 to 16.0)</td>
<td>1.70 (1.21 to 2.39)</td>
<td>.002</td>
</tr>
<tr>
<td>Overall</td>
<td>100/577 15.5 (8.0 to 27.9)</td>
<td>47/462 6.7 (1.6 to 24.1)</td>
<td>1.81 (1.30 to 2.50)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>test, ( Q )</td>
<td>8.71</td>
<td>6.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P )</td>
<td>.003</td>
<td>.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( I^2 )</td>
<td>88.5%</td>
<td>84.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### High-grade

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib</th>
<th>Control</th>
<th>Relative Risk</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demetri (2006)</td>
<td>3/202 1.5 (0.5 to 4.5)</td>
<td>0/102 0.0</td>
<td>3.55 (0.19 to 68.1)</td>
<td>.40</td>
</tr>
<tr>
<td>Motzer (2009)</td>
<td>13/375 3.5 (2.0 to 5.9)</td>
<td>4/360 1.1 (0.4 to 2.9)</td>
<td>3.12 (1.03 to 9.48)</td>
<td>.05</td>
</tr>
<tr>
<td>Barrios (2010)</td>
<td>1/238 0.4 (0.1 to 2.9)</td>
<td>0/244 0.0</td>
<td>3.08 (0.13 to 75.1)</td>
<td>.49</td>
</tr>
<tr>
<td>Raymond (2011)</td>
<td>2/86 2.3 (0.6 to 8.8)</td>
<td>0/85 0.0</td>
<td>4.94 (0.24 to 101.5)</td>
<td>.30</td>
</tr>
<tr>
<td>Overall</td>
<td>19/901 2.6 (1.7 to 4.0)</td>
<td>4/791 0.8 (0.4 to 1.9)</td>
<td>3.30 (1.29 to 8.45)</td>
<td>.01</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>test, ( Q )</td>
<td>5.48</td>
<td>1.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P )</td>
<td>.140</td>
<td>.672</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( I^2 )</td>
<td>45.3%</td>
<td>0.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Richards et al. JCO 2011;29:3450-3456
### Table 5. Special analysis of grouped-term organ system adverse events.

<table>
<thead>
<tr>
<th>Grouped adverse event, n. (%)</th>
<th>Any AE</th>
<th>≥Grade3</th>
<th>SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cardiac</td>
<td>116 (22.1)</td>
<td>50 (9.5)</td>
<td>41 (7.8)</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>70 (13.3)</td>
<td>12 (2.3)</td>
<td>11 (2.1)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>38 (7.2)</td>
<td>30 (5.7)</td>
<td>26 (4.9)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>18 (3.4)</td>
<td>7 (1.3)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>9 (1.7)</td>
<td>3 (0.6)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Any respiratory</td>
<td>363 (69.0)</td>
<td>54 (10.3)</td>
<td>34 (6.5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>222 (42.2)</td>
<td>26 (4.9)</td>
<td>11 (2.1)</td>
</tr>
<tr>
<td>Cough</td>
<td>137 (26.0)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>67 (12.7)</td>
<td>55 (10.5)</td>
<td>52 (9.9)</td>
</tr>
<tr>
<td>Any grouped renal impairment</td>
<td>174 (33.1)</td>
<td>38 (7.2)</td>
<td>32 (6.1)</td>
</tr>
<tr>
<td>Increased serum</td>
<td>127 (24.1)</td>
<td>14 (2.7)</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>28 (5.3)</td>
<td>23 (4.4)</td>
<td>22 (4.2)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>20 (3.8)</td>
<td>6 (1.1)</td>
<td>7 (1.3)</td>
</tr>
</tbody>
</table>

Techniques to Improve the Identification of Cardiotoxicity: Beyond Ejection Fraction

- Biomarkers
- Strain Imaging
Troponins and Development of Cardiotoxicity

Cardiac event free rate (%) vs. months

TnI -/-

TnI +/-

TnI +/+
Strain Imaging to Diagnose Chemotherapy Induced Cardiomyopathy

- Measure of myocardial deformation

- Identification of subclinical LV dysfunction prior to EF changes

- Potential role for early cardiovascular intervention
Abnormal Strain and Trastuzumab Exposure

Hare, Am Heart J, 2009.
Abnormal Strain and Trastuzumab

A

Baseline
GLS -20.1%
EF 61%

F/U 1
GLS -17.0% (Δ -15.4%)
EF 55%

F/U 2
GLS -16.1%
EF 49%

B

GLS 21.9%
EF 62%

GLS 16.6% (Δ -24%)
EF 51%

GLS 20.2%
EF 58%
Prevention of Chemotherapy Induced Cardiomyopathy

A

B

Cardinale et al. Circ. 2006.
Prevention of Chemotherapy Induced Cardiomyopathy: PRADA

A. Effect of Candesartan Treatment
Difference in change in LVEF (95% CI) from baseline to EOS

Sample
- n = total/candesartan/not candesartan
  - All patients (n = 109/57/52)
  - Age > median (n = 55/29/27)
  - Age ≤ median (n = 54/29/25)
  - Current smoker (n = 19/11/8)
  - Not current smoker (n = 90/46/44)
  - Hypertension (n = 8/8/2)
    - No hypertension (n = 101/51/50)
  - BMI > median (n = 51/20/31)
    - BMI ≤ median (n = 58/37/21)
  - Trastuzumab (n = 25/13/12)
    - No trastuzumab (n = 84/44/40)
  - No radiation (n = 24/14/10)
    - Left sided radiation (n = 40/23/17)
    - Right sided radiation (n = 45/20/25)

B. Effect of Metoprolol Treatment
Difference in change in LVEF (95% CI) from baseline to EOS

Sample
- n = total/metoprolol/not metoprolol
  - All patients (n = 109/54/55)

Coronary Artery Disease, Myocardial Infarction, and Peripheral Arterial Disease
Therapies Associated With Vascular Disease

- Radiation

- Tyrosine Kinase Inhibitors
  - Nilotinib
  - Ponatinib
CV Complications of Radiation

- Important part of treatment for many cancers including breast, lung and lymphoma
- Increased risk with increased dose (Gray)
- Complications typically seen 5-10 years post exposure
- Complications include:
  - Premature CAD
  - Carotid Disease
  - Valvular disease (especially aortic and mitral disease)
  - Pericardial and myocardial disease
  - Heart failure
  - Conduction abnormalities
Risk Factors for Radiation Induced CV Disease

- Total dose >30 Gy or fractioned dose >2Gy/day
- Heart volume exposed
- Time since exposure
- Adjunctive chemo/hormone therapy
- Presence of CV risk factors (diabetes, obesity, smoking, hypertension, dyslipidemia)
- Younger age
Coronary Events in Breast Cancer 
Radiation Therapy

Percent Increase in Rate of Major Coronary Events (95% CI)

- Increase per gray, 7.4% (95% CI, 2.9–14.5)
- P<0.001

Mean Dose of Radiation to Heart (Gy)

Cumulative Risk of Death from Ischemic Heart Disease (%)

- Radiotherapy with mean heart dose of 10 Gy
- Radiotherapy with mean heart dose of 3 Gy
- No radiotherapy

Age (yr)

Darby, et al. NEJM 2013

MOFFITT CANCER CENTER

USF HEALTH
Radiation and Carotid Artery Disease

Huang et al., Rad Onc, 2013

Halak et al, Eur J Vasc Enodvasc Surg, 2002
## ENESTnd 3-Yr Update

Hematologic AEs and Biochemical Abnormalities

<table>
<thead>
<tr>
<th>Grade 3/4 AEs, %</th>
<th>Nilotinib 300 mg BID (n = 279)</th>
<th>Nilotinib 400 mg BID (n = 277)</th>
<th>Imatinib 400 mg QD (n = 280)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>11.8</td>
<td>10.8</td>
<td>21.4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10.4</td>
<td>12.3</td>
<td>8.9</td>
</tr>
<tr>
<td>Anemia</td>
<td>3.9</td>
<td>4.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Lipase increase</td>
<td>7.5</td>
<td>7.9</td>
<td>3.9</td>
</tr>
<tr>
<td>ALT increase</td>
<td>4.3</td>
<td>9.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Total bilirubin increase</td>
<td>3.9</td>
<td>7.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>6.1</td>
<td>5.4</td>
<td>0</td>
</tr>
</tbody>
</table>

### Nilotinib Toxicities

- Prolongation of QTC and vascular adverse events
- Coronary events
- Peripheral Arterial Occlusive Disease – PAOD

Nilotinib and Cardiovascular Events

No of Patients: 28/279

# CML and Ponatinib: Cardiovascular Events

<table>
<thead>
<tr>
<th></th>
<th>Serious AE %</th>
<th>AE %</th>
<th>Serious AE %</th>
<th>AE %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Peripheral Vascular</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Venous Thromboembolism</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total Vascular Occlusion</td>
<td>11</td>
<td>16</td>
<td>17</td>
<td>29</td>
</tr>
</tbody>
</table>

US Ponatinib Insert (7/23/12)  
Median Follow up: 12 Mos  
(340 pt-years)

PACE Trial (9/3/13)  
Medial Follow Up: 24 Mos  
(578 pt-years)

5-Fluorouracil Induced Myocardial Ischemia and Infarction

- Cheat pain is a common symptom among patients treated with 5-FU
- Etiology is thought secondary to vasospasm though myocarditis is also possible
- Risk increased with continuous infusions
- Nitrates of calcium channel blockers may prevent episodes
QT Interval Prolongation and Arrhythmias
Malignancy and QT Prolongation

CO-EXISTING CONDITIONS
- Older age
- Female
- Hypothyroid
- Congenital Long QT Syndrome
- Cardiac disease
- LV dysfunction
- Cardiac ischemia
- Bradycardia
- Other conduction disease

CANCER THERAPY
- Taxanes
- Cyclophosphamide
- Epothilones
- Thalidomide
- Interferons
- Interleukin-2
- Multi-targeted tyrosine kinase inhibitors
  - Sunitinib
  - Dasatinib
  - Vandetanib*
- Arsenic trioxide
- Tipifarnib*
- Enzastaurin*
- Combretastatin*
*not FDA approved

CANCER THERAPY-RELATED
- Dehydration/electrolyte imbalance
- Nausea and emesis
- Diarrhea
- Diuresis
- Poor oral intake
- Renal insufficiency
- Hepatic dysfunction
- Poorly controlled diabetes

CONCOMITANT MEDICATIONS
- Antidepressants
- Anti-emetics
- Antibiotics
- Antipsychotics
- Antifungals
- Antihistamines
- Methadone

PROLONGED QT
# Chemotheapry Associated with QT Prolongation

<table>
<thead>
<tr>
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<tr>
<td>• Sunitinib</td>
<td>&lt;1-3</td>
<td>++</td>
</tr>
<tr>
<td>• Vandetinib</td>
<td>15-18</td>
<td>+</td>
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<td>1-3</td>
<td>++</td>
</tr>
<tr>
<td>• Dasatinib</td>
<td>&lt;1</td>
<td>++</td>
</tr>
<tr>
<td><strong>Histone Deacetylase Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Vorinostat</td>
<td>3.5-6</td>
<td>+</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Aresenic</td>
<td>26-93</td>
<td>+</td>
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</tbody>
</table>
Cancer and Atrial Fibrillation

Chemotherapy and the Risk of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Risk of Atrial Fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>13.3</td>
</tr>
<tr>
<td>Melphalan</td>
<td>11.8</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>10.3</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>8.2</td>
</tr>
<tr>
<td>5FU + Cisplatin</td>
<td>6.5</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>5</td>
</tr>
</tbody>
</table>

Hypertension
VEGF Inhibitors and Hypertension

Mechanism of VEGF Induced Hypertension

http://omicsonline.org/JGSGTimages/2157-7412-2-105-g001.html
VEGF Inhibitors and Hypertension: Marker of Efficacy?

VEGF Inhibitor Induced Hypertension: Treatment Options

- **First Line Therapies**
  - ACE Inhibitors/Angiotensin Receptor Blockers
  - Dihydropyridine Calcium Channel Blockers (CCBs)

- **Second Line Therapies**
  - Beta blockers and Diuretics

- **Novel/Investigational Therapies**
  - Nitric Oxide Donating Medications
  - Endothelin-1 Receptor Antagonists

Kaplan-Meier Estimate of Overall Survival Stratified by Antihypertensive Use

Valvular Heart Disease
Valvular Heart Disease: Etiology and Risk Factors

- Most often associated with chest radiation
- May also be associated with anthracycline exposure
- Aortic and mitral valves most commonly affected
- Regurgitant lesions more common than stenotic
- Presents 10+ years post treatments
Prevalence of Valvular Abnormalities in Hodgkin Lymphoma Survivors

Monitoring and Prevention of Cardiovascular Disease in Cancer Patients and Survivors
Prevention of Cardiovascular Disease in Cancer Patients: Learn your ABCs

- A: Awareness of potential CV dysfunction; aspirin; Ankle-brachial index
- B: Blood pressure control
- C: Cholesterol control; cigarette avoidance
- D: Diabetes control; healthy dieatary choices
- E: Exercise. Echo. EKG.
Conclusions

- Cardiovascular toxicity has significant impact on both cancer patients and survivors

- LV dysfunction, arrhythmias, ischemia, hypertension and valvular dysfunction are commonly observed toxicities

- Radiation therapy has significant impact on the CV system

- Biomarkers and strain imaging may help with the early diagnosis of cardiotoxicity
Thank You