ONCO-CARDIOLOGY: Optimizing Outcomes

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University Hospitals

Ohio ACC Summit 2016
Onco-Cardiology Mission

• To achieve better outcomes of cancer patients by providing cardiovascular care before, during and after cancer treatment.
Content

• The Impact of CVD and Cardiotoxicity
• Mechanisms of Selected Cardiotoxicities
• Risk Stratification and Prevention
• Newer Modalities for Surveillance
• Interventions
• UH Protocols
Burden of CVD by Cancer Type

CVD Management in Cancer Patients

# Impact of Cardiotoxicity

## Short term
- Treatment interruption
- Treatment discontinuation
- Dose reductions
- Heart dysfunction/failure
- Hypertension
- Acute coronary symptoms
- Pulmonary hypertension
- Thrombosis
- PAD/stroke
- Arrhythmias

## Long term
- Cardiomyopathy
- End-stage heart failure
- Valvular heart disease
- Pericardial disease
- Heart transplant
- Heart pumps
- Early death
• 5-41% of patients on trastuzumab undergo interruptions at some time for cardiotoxicity.

## Relationship between cardiac events and discontinuation

### Table 4 Cardiovascular events occurring 45 days before or after last trastuzumab treatment

<table>
<thead>
<tr>
<th></th>
<th>Early discontinuation no. = 239 (41 %)</th>
<th>Completion group no. = 346 (59 %)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Any cardiovascular</strong></td>
<td>60</td>
<td>25.1</td>
<td>25</td>
</tr>
<tr>
<td>Heart failure/</td>
<td>45</td>
<td>18.8</td>
<td>14</td>
</tr>
<tr>
<td>cardiomyopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>13</td>
<td>5.4</td>
<td>&lt;11</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>19</td>
<td>7.9</td>
<td>12</td>
</tr>
<tr>
<td>events(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Individuals may be in multiple sub-categories of cardiovascular events, therefore, numbers of specific events will not sum to the number presented as Any cardiovascular  
\(^b\) Cell values less than 11 were not reported per SEER-Medicare DUA to protect the privacy of human subjects  
\(^c\) Including acute myocardial infarction, acute coronary syndrome, angina, ventricular fibrillation, cardiac arrest, stroke, transient ischemia accident, pulmonary embolism, deep vein thrombosis, or acute embolism.
Effect of Discontinuation on Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete-No CV</td>
<td>321</td>
</tr>
<tr>
<td>Incomplete-No CV</td>
<td>174</td>
</tr>
<tr>
<td>Complete-CV</td>
<td>25</td>
</tr>
<tr>
<td>Incomplete-CV</td>
<td>52</td>
</tr>
</tbody>
</table>

Survival was evaluated starting from the date 1 year after initiating trastuzumab treatment. CV cardiovascular events.

Fig. 1 Survival among patients receiving trastuzumab treatment according to completion of trastuzumab treatment and cardiovascular events.

Association of discontinuation CV events and death

Table 5  Factors associated with all-cause mortality

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard ratio (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete trastuzumab</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Reference</td>
</tr>
<tr>
<td>No (Early discontinuation)</td>
<td>1.74 (0.94–3.23)</td>
</tr>
<tr>
<td><strong>Any CV event in 45 days before or after last trastuzumab</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.54 (1.87–6.68)</td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
</tr>
<tr>
<td><strong>Age groups (years)</strong></td>
<td></td>
</tr>
<tr>
<td>67–69</td>
<td>Reference</td>
</tr>
<tr>
<td>70–74</td>
<td>0.88 (0.46–1.68)</td>
</tr>
<tr>
<td>75–94</td>
<td>0.38 (0.15–0.95)</td>
</tr>
</tbody>
</table>
Incidence of HF/LVD after Anthracyclines ± Trastuzumab

<table>
<thead>
<tr>
<th></th>
<th>All Cancer Patients</th>
<th>Anthracycline + Trastuzumab (n = 431)</th>
<th>Anthracycline (n = 5,257)</th>
<th>Trastuzumab (n = 437)</th>
<th>Other Chemotherapy (n = 2,712)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observed cumulative incidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>7.2</td>
<td>16.4*</td>
<td>7.7‡</td>
<td>15.7*</td>
<td>7.8</td>
</tr>
<tr>
<td>2 years</td>
<td>12.3</td>
<td>23.8*</td>
<td>11.9</td>
<td>20.7*</td>
<td>12.4</td>
</tr>
<tr>
<td>3 years</td>
<td>16.9</td>
<td>28.2*</td>
<td>15.3‡</td>
<td>26.7*</td>
<td>17.0</td>
</tr>
<tr>
<td><strong>Adjusted cumulative incidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>7.5</td>
<td>22.0*</td>
<td>9.8*</td>
<td>16.7*</td>
<td>8.4*</td>
</tr>
<tr>
<td>2 years</td>
<td>13.3</td>
<td>33.2*</td>
<td>15.3*</td>
<td>23.2*</td>
<td>13.7*</td>
</tr>
<tr>
<td>3 years</td>
<td>18.7</td>
<td>41.9*</td>
<td>20.2‡</td>
<td>32.1*</td>
<td>19.2</td>
</tr>
</tbody>
</table>

Chen et al. JACC Vol. 60, No. 24, 2012
CV Complications of VGEF Inhibitors

Hall et al. JACCHF Feb 2013
Cancer Survivors in the US


AACR Cancer Progress Report 2013
Incidence of CVD in 10-year Breast Cancer Survivors

N=4400

Breast Cancer Survivors CV Mortality

Breast Cancer Survivors CV Mortality

Source: Breast Cancer Res © 2011 BioMed Central Ltd
Mortality Among Childhood Cancer Survivors

- Subs Malignancy: 44%
- External: 17%
- Cardiac: 13%
- Pulmonary: 6%
- Other: 19%

Non-Recurrence Deaths = 1065

N = 20,400
Deaths: 2,2080
Years Follow-up: 20

Types of Cardiotoxicity

<table>
<thead>
<tr>
<th>Type I CRCD</th>
<th>Type II CRCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular death</td>
<td>Cellular dysfunction</td>
</tr>
<tr>
<td>Biopsy changes</td>
<td>No Biopsy changes</td>
</tr>
<tr>
<td>Cumulative dose-related</td>
<td>Not dose-related</td>
</tr>
<tr>
<td>Oxidative stress/DNA damage</td>
<td>Erbb2-signaling</td>
</tr>
<tr>
<td>Permanent</td>
<td>Reversible</td>
</tr>
</tbody>
</table>

**Model:** doxorubicin  
**Model:** Trastuzumab

Courtesy of Michael Ewer, MD
# Chemotherapy-Induced Cardiotoxicity

<table>
<thead>
<tr>
<th>Agent</th>
<th>LVD (%)</th>
<th>HTN (%)</th>
<th>ACS (%)</th>
<th>Arrhythmia (5)</th>
<th>Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>3-26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>7-28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>2-8</td>
<td></td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td></td>
<td>0.5-5</td>
<td>0.1-31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>1.7-3</td>
<td>4-35</td>
<td>1.5-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>2-40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>2.7-11</td>
<td>5-30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>0.5-1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td></td>
<td>17-43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td></td>
<td>2.3</td>
<td></td>
<td>3.9-11</td>
</tr>
<tr>
<td>Fluorouracil (5-FU)</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td>2-43</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib (Velcade)</td>
<td>2-5</td>
<td></td>
<td>3-9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
<td></td>
<td></td>
<td>8.5-13%</td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td></td>
<td></td>
<td></td>
<td>0.2-55%</td>
<td></td>
</tr>
<tr>
<td>Lenalidomide (Revlimid)</td>
<td></td>
<td></td>
<td></td>
<td>3-75</td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>1.5-2.2</td>
<td></td>
<td></td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Yeh ET and Bickford CL. JACC 2009
Doxorubicin Dose and HF

HF Incidence %

Cumulative doxorubicin dose

Adapted from Ewer et al. JCO 1984;2:112-117.
Dose Biopsy Grade and HF Incidence

Cardiac biopsy grade versus cumulative doses of Doxorubicin

IV Doxorubicin every 3-4 weeks. Biopsy specimens every 3-4 weeks.

- Mackay—MDAH
- Billingham—Stanford

HF Incidence %

Cumulative dose of Doxorubicin (mg/m²)

200–400: n=8, n=18
401–500: n=22, n=8
>500: n=3, n=7

*Risk of CHF

Pathology of Adriamycin Cardiotoxicity
Risk of IHD with Radiation Dose

N = 2168
963 with MACE

Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

Darby et al. NEJM March 2013
Incidence of CVD after Radiation Therapy

Figure 2. Cumulative incidence of cardiac disorders among childhood cancer survivors by average cardiac radiation dose. Reproduced from Mulrooney et al175 with permission from BMJ Publishing Group Ltd. Copyright © 2009, BMJ Publishing Group Ltd.
Radiation Coronary Disease

- LMT 1.8:1
- Ostial LAD
- Ostial RCA
- >30 Gy
- Younger age
- Longer time since exposure

Radiation Pericarditis

• ≥35Gy- 20-40%
  <30 Gy- 2.5%
• 4 months-years
• Acute (effusion)
• Delayed Acute (effusive-constrictive)
• Delayed Chronic
• Pancarditis >60 Gy

Radiation Cardiomyopathy

- 16% at >20 Gy
- Systolic dx with Chemo
- Perfusion defects common
- Longer time since exposure
- Younger age

Radiation Valvular Heart Disease

- $\geq 35\text{Gy}$
- 11-16 years
- Mitral and Aortic
- RVOT stenosis

Contents

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Risk factors for LVD/CHF with Trastuzumab

SEER Analysis of 1664 women

J Am Heart Assoc. 2014; 3: e000472
## Common Anthracycline Regimens and Cancers

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Anthracycline Regimens</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Doxorubicin 50-60 mg/m² × 4-6 cycles</td>
<td>Increased cardiotoxicity with trastuzumab (11)</td>
</tr>
<tr>
<td></td>
<td>Epirubicin 75-100 mg/m² × 4-8 cycles</td>
<td>Bolus over 15 min</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Doxorubicin 75-90 mg/m² × 6-8 cycles</td>
<td>Continuous infusion over 48-72 h or bolus over 15 min + dextrazoxane</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Doxorubicin 40-50 mg/m² × 6-8 cycles</td>
<td>Continuous infusion over 48-72 h or bolus over 15 min</td>
</tr>
<tr>
<td>Pediatric leukemia</td>
<td>Doxorubicin 30 mg/m² × 10 cycles</td>
<td>Bolus over 30 min ± dextrazoxane</td>
</tr>
</tbody>
</table>

Yeh ET et al. JACC 2015
Primary Prevention of Anthracycline Cardiotoxicity

<table>
<thead>
<tr>
<th>Prevention Strategy</th>
<th>Cost*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous doxorubicin infusion (48–72 h)</td>
<td>$67/50 mg†</td>
<td>Effective in cardioprotection in sarcoma and lymphoma, but not in the pediatric population</td>
</tr>
<tr>
<td>Liposomal doxorubicin</td>
<td>$2,851/50 mg</td>
<td>FDA-approved for ovarian cancer, AIDS-related Kaposi sarcoma, and multiple myeloma, after failure of at least 1 prior therapy</td>
</tr>
<tr>
<td>Dexrazoxane</td>
<td>$362/500 mg</td>
<td>FDA-approved only for women with metastatic breast cancer who received at least 300 mg/m² doxorubicin and need additional doxorubicin to maintain tumor control</td>
</tr>
<tr>
<td>ACEI/ARB/β-blockers</td>
<td>$4/month</td>
<td>Unknown whether they were cardioprotective or simply changed hemodynamics</td>
</tr>
</tbody>
</table>

*2014 Walmart pharmacy prices. †May be higher, depending on hospital stay or infusion pump care costs.

ACEI = angiotensin-converting enzyme inhibitor; AIDS = acquired immune deficiency syndrome; ARB = angiotensin receptor blocker; FDA = U.S. Food and Drug Administration.

Yeh ET et al. JACC 2015
The **OVERCOME** Trial

**Figure 1** Flow Diagram of the OVERCOME Study

A total of 81% of all eligible patients during a 2-year period were enrolled in the study and were randomized to the intervention or control group. ACEI = angiotensin-converting enzyme inhibitor.

Bosch et al. JACC June 2013
The OVERCOME Trial

![Graph showing changes in EF (Ejection Fraction) from baseline to 6 months in Intervention and Control Groups.](image)

**Figure 2** Change From Baseline in LVEF in Acute Leukemia Patients Undergoing Chemotherapy in the Intervention and Control Groups

While no differences were observed in the intervention group, patients in the control group had a 6.7% absolute decrease in their mean left ventricular ejection fraction (LVEF), $p = 0.025$, with all but 3 patients having some degree of LVEF reduction. Values are mean ± SEM.

**Table 4** Clinical Endpoints

<table>
<thead>
<tr>
<th>Clinical Endpoint</th>
<th>Enalapril + Carvedilol</th>
<th>Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature end of the study (%)</td>
<td>3 (6.7)</td>
<td>11 (24.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Total mortality (%)</td>
<td>3 (6.7)</td>
<td>8 (17.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Death or heart failure (%)</td>
<td>3 (6.7)</td>
<td>10 (22.2)</td>
<td>0.036</td>
</tr>
<tr>
<td>Death, heart failure or final LVEF&lt;45% (%)</td>
<td>3 (6.7)</td>
<td>11 (24.4)</td>
<td>0.020</td>
</tr>
<tr>
<td>≥10% decrease in LVEF with a final LVEF&lt;50% (%)</td>
<td>2 (4.8)</td>
<td>2 (5.4)</td>
<td>0.90</td>
</tr>
<tr>
<td>Heart failure or ≥10% decrease in LVEF (%)</td>
<td>4 (9.5)</td>
<td>7 (19)</td>
<td>0.22</td>
</tr>
<tr>
<td>Severe adverse events* (%)</td>
<td>9 (20)</td>
<td>15 (33)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Bosch et al. JACC June 2013
Cardioprotective effects of BB

Seicean et al. Circ Heart Fail. May 2013
Carvedilol for cardioprotection

Kalay et al. JACC Dec 2006
Dexrazoxane for Cardioprotection

Lipschultz et al. Lancet Oncol. 2010 October
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Strain Echocardiography

Thavendiranathan et al. *Circ Cardiovasc Imaging* 2013
Decreases in strain predict cardiotoxicity

Figure 4: The Utility of Early Strain Changes to Predict Subsequent Cardiotoxicity

The images demonstrate a "bull's eye" plot of strain values for each of the 17 myocardial segments. A patient receiving cytotoxic chemotherapy had normal baseline strain and left ventricular (LV) ejection fraction (EF) at first. Six months into therapy, the LVEF dropped by 6% but did not meet criteria for cardiotoxicity. However, the peak systolic global longitudinal strain (GLS) fell by 15.4% (a significant change based on the literature). Then, by 12 months there was a clinically significant fall in LVEF meeting the criteria for cardiotoxicity. See Online Videos 1, 2, and 3 for 4-chamber movie images demonstrating the changes in function. LVEF was calculated using the Biplane Simpson’s method.

Thavendiranathan et al. JACC July 2014
Cardiac MRI and Cardiotoxicity Detection

Table 6. Potential Clinical Uses of CMR for Assessment of Cardiac Consequences of Cancer Chemotherapy at Various Stages of Toxicity

<table>
<thead>
<tr>
<th>Stage</th>
<th>EGE</th>
<th>T2</th>
<th>T1</th>
<th>ECV</th>
<th>Arterial Stiffness</th>
<th>LGE</th>
<th>LV Volume</th>
<th>LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early injury</td>
<td>√</td>
<td>√</td>
<td>+/−</td>
<td>+/−</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity during or early post-therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Late cardiotoxicity</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Thavendiranathan et al. *Circ Cardiovasc Imaging* 2013
ROC curve for cTnl as marker of cardiotoxicity.

BNP predicts cardiotoxicity and death in patients with cancer

Skovgaard et al. PLOS one 2014
Contents

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Response of Anthracycline-Induced Cardiomyopathy to HF therapy

45% of patients did not respond

Survival of Responders vs. Non-responders

Figure 2
Cumulative Cardiac Event Rate During the Study Follow-Up

2-year Kaplan-Meier analysis for major adverse cardiac events in the 3 study groups. \( p = 0.0003 \) (log-rank test).

Incidence, Predictors, and Impact on Survival of Left Ventricular Systolic Dysfunction and Recovery in Advanced Cancer Patients

Guilherme H. Oliveira, MD\textsuperscript{a,\,*}, Siddarth Mukerji, MD\textsuperscript{b}, Adrian V. Hernandez, MD\textsuperscript{c,d}, Marwan Y. Qattan, MD\textsuperscript{a}, Jose Banchs, MD\textsuperscript{e}, Jean-Bernard Durand, MD\textsuperscript{e}, Cezar Iliescu, MD\textsuperscript{e}, Juan Carlos Plana, MD\textsuperscript{f}, and W.H. Wilson Tang, MD\textsuperscript{f}

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<table>
<thead>
<tr>
<th>Patients Appropriate for Onco-Cardiology Referral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREEXISTING HEART DISEASE</strong></td>
</tr>
<tr>
<td>1. CAD (stents, CABG, previous myocardial infarction)</td>
</tr>
<tr>
<td>2. History of heart failure</td>
</tr>
<tr>
<td>4. Valvular heart disease (&gt; mild)</td>
</tr>
<tr>
<td>7. Peripheral vascular disease</td>
</tr>
<tr>
<td>8. Uncontrolled hypertension</td>
</tr>
<tr>
<td>9. Cardiac tumors</td>
</tr>
<tr>
<td>9. Arrhythmias</td>
</tr>
</tbody>
</table>
## CARDIOVASCULAR EVALUATION AND TESTING

### SUSPICION OF CAD
1. High suspicion (abnormal stress test, CT arteriogram, CT calcium scoring >1000, classic angina, anginal equivalent): heart catheterization
2. Intermediate suspicion: CT arteriogram with heart flow
3. Low suspicion (rule out CAD for history of previous chest radiation without other risk factors or symptoms): CT calcium scoring

### HISTORY OF CHEST RADIATION
1. Calcium CT scoring (if asymptomatic)
2. CTA with heartflow or heart catheterization depending on degree of CAD suspicion

### LOW EF
1. Repeat echocardiogram if outside study
2. Heart catheterization
3. Cardiac MRI with DGE

### ARRHYTHMIA/PALPITATIONS
1. Ziopatch
2. Holter monitor
3. Thyroid function tests

### VASOSPASM WITH 5-FU
- Heart catheterization before next dose

### ALL PATENTS
- History
- Physical examination
- EKG
- Complete 2D and 3D echocardiogram with strain
- NT pro-BNP
- Lipid profile

### MULTIPLE MYELOMA UNDERGOING STEM CELL TRANSPLANT
- Cardiac MRI with DGE to rule out cardiac amyloidosis
- Consider endomyocardial biopsy if MRI equivocal

### HISTORY OF CHEST RADIATION
1. Calcium CT scoring (if asymptomatic)
2. CTA with heartflow or heart catheterization depending on degree of CAD suspicion

### ARRYTHMIA/PALPITATIONS
1. Ziopatch
2. Holter monitor
3. Thyroid function tests

### VASOSPASM WITH 5-FU
- Heart catheterization before next dose

### KNOWN CAD, STENT, CABG OR OLD MI
1. CTA with heartflow if no stent or CABG
2. Heart catheterization if previous stent or CABG or symptomatic
**Cardiotoxicity prophylaxis in high-risk patients**

**GROUP A**
Patients who will receive anthracyclines, HER2 inhibitors, VGEF inhibitors or stem cell transplant and any of the below:
- Abnormal left ventricular systolic function (EF<50% or global longitudinal strain<-18%)
- History of previous anthracycline therapy
- History of CAD, stent, CABG or old MI
- History of recovered EF
- History of heart failure in the past

1. **Carvedilol**- start at 3.125 BID or consider Coreg CR 10mg at bedtime if patient SBP is <110 mmHg
2. **Ramipril**- start at 2.5 mg daily. Give in addition to carvedilol if BP allows
3. **Statin**- Rosuvastatin 5 mg or pravastatin 20 mg
4. **Dexrazoxane**- in patients that need additional anthracycline therapy.
5. **Use of liposomal doxorubicin**- in patients that need anthracycline therapy.

**GROUP B**
Patients who will receive VGEF inhibitors and Hypertension (BP >140/90)

1. **Nifedipine XL**- start at 30 mg a day and go up to 120 mg
2. **Telmisartan +/- HCTZ**- only use in patients without nephrectomy and with normal renal function
3. **Carvedilol**- start at 3.125 and escalate

**GROUP C**
Patients who receive 5-FU, capecitabine or bevacizumab with:
- Known CAD
- History of vasospasm

1. **Nifedipine XL 30-120 mg**- Start 24 h before 5-FU infusion and stop 48h following end of infusion
2. **Isosorbide mononitrate 30-120 mg**- Start 24h before 5FU infusion and stop 48h following end of infusion.
3. For patients on oral capecitabine, continue either or both throughout treatment period depending on blood pressure.
Cardiotoxicity surveillance during HER-2 antagonist therapy

- **Normal baseline echo (EF >50% or GLS >-18%) and non-high risk CV risk assessment**
  - If normal, Repeat echo, BNP and clinical assessment every 3 months
  - Repeat last echo 3 months following end of treatment

- **Normal baseline echo and high risk CV profile**
  1. Repeat echo, BNP and clinical assessment in 1 month
  2. If echo, BNP are normal and patient is asymptomatic, repeat echo, BNP and clinical assessment in 3 months
  3. If echo or BNP are abnormal or patient has HF symptoms, repeat echo, BNP and clinical assessment before each cycle at 1 month intervals

- **Abnormal baseline echo (EF <50% or GLS <-18%)**
  - Repeat echo, BNP and clinical assessment before each cycle at 1 month intervals
Cardiotoxicity surveillance during anthracycline therapy

**Normal baseline echo (EF >50% or GLS >-18%) and non-high risk CV risk assessment**

1. Repeat echo, BNP, and clinical assessment at 1 month and then every 3 months
2. Perform troponin I measurement immediately after first cycle and at 3 months (doesn’t make sense since this is under low risk – no coverage if asymptomatic)
3. Repeat echos at 3 months, 6 months, 1 year, 3 years, 5 years and 10 years after end of treatment if asymptomatic and normal EF maintained throughout treatment

**Normal baseline echo and high risk CV profile**

1. Repeat echo, BNP, and clinical assessment in 1 month
2. If echo, BNP are normal and patient is asymptomatic, repeat echo, (BNP, troponin – won’t be covered if asymptomatic) I and clinical assessment in 3 months
3. If echo or BNP are abnormal or patient has HF symptoms, repeat echo, BNP, and clinical assessment before each cycle and troponin I immediately after each cycle
4. Repeat echos at 3 months, 6 months, 1 year, 3 years, 5 years and 10 years after end of treatment if asymptomatic and normal EF maintained throughout treatment.

**Abnormal baseline echo (EF <50% or GLS <-18%)**

1. Repeat echo, BNP, and clinical assessment before each cycle at 1 month intervals
2. Perform troponin I measurement immediately after each cycle
3. Repeat echos at 3 months, 6 months, and then annually
Management of cardiotoxicity from HER-2 antagonists

≥15% drop in GLS and or >10 points in EF, but EF > 50% and no HF symptoms and normal BNP

1. **Continue HER2 inhibitor**
2. Start carvedilol or Coreg CR (in patients with low BP), at lowest dose as 1st line of therapy
3. If BP allows, start Ramipril (2.5-10 mg a day)
4. Repeat echo, BNP and clinical assessment prior to each cycle

Drop in EF to <50% but >40% without HF symptoms or elevated BNP

1. **Continue HER2 inhibitor**
2. Start carvedilol or Coreg CR (in patients with low BP), at lowest dose as 1st line of therapy
3. If BP allows, start Ramipril (2.5-10 mg/day) or valsartan/sacubitril
4. Start spironolactone (12.5-50 mg/day)
5. Consider ivabradine for HR in patients who cannot tolerate high dose carvedilol
6. Repeat echo, BNP and clinical assessment prior to each cycle

Drop in EF to <40% and/or HF symptoms and abnormal BNP

1. **Stop HER 2 inhibitor**
2. Start carvedilol or Coreg CR (in patients with low BP), at lowest dose as 1st line of therapy
3. If BP allows, start Ramipril (2.5-10 mg/day) or valsartan/sacubitril
4. Start spironolactone (12.5-50 mg/day)
5. Start furosemide for volume control
6. Consider digoxin, hydralazine and nitrates
7. Consider ivabradine for HR control in patients who cannot tolerate high dose carvedilol
8. Repeat echo, BNP and clinical assessment monthly until HF resolves and EF returns to >40%
9. Resume HER2 inhibitor when HF resolves and EF returns to >40%
Cardiotoxicity surveillance during VEGF therapy and stem cell transplant

**VEGF INHIBITORS**

1. Normal baseline echo and non-high CV risk profile and BP < 140/90 mmHg
   1. Repeat echo in 3 months.
   2. If 3 month echo is normal, no more echos
   3. Repeat echo if patient becomes symptomatic or develops S/S of HF at any point throughout treatment

2. High risk and/or abnormal baseline echo
   Repeat echo at the end of therapy

**HSCT**

1. Obtain pre-transplant echo (post any cardiotoxic treatment and within 1 month prior to transplant)
2. Repeat echo 1 month following discharge from transplant
3. If previous anthracycline therapy, follow monitoring schedule above
Management of cardiotoxicity from Anthracyclines

1. ≥15% drop in GLS and or >10 EF points, but EF > 50% and no HF symptoms and normal BNP

1. Continue anthracyclines
2. Start carvedilol or Coreg CR (in patients with low BP), at lowest dose as 1st line of therapy
3. If BP allows, start Ramipril (2.5-10 mg a day)
4. Repeat echo, BNP and clinical assessment prior to each cycle

1. Drop in EF to <50% but >40% without HF symptoms or elevated BNP

1. Hold anthracyclines
2. Start carvedilol or Coreg CR (in patients with low BP), at lowest dose as 1st line of therapy
3. If BP allows, start Ramipril (2.5-10 mg/day) or valsartan/sacubitril
4. Start spironolactone (12.5-50 mg/day)
5. Consider ivabradine for HR in patients who cannot tolerate high dose carvedilol
6. Repeat echo, BNP and clinical assessment in 1 month to evaluate LV recovery
7. Consider rechallenging with liposomal anthracycline or concomitant dexrazoxane

1. Drop in EF to <40% and/or HF symptoms and abnormal BNP

1. Stop anthracyclines
2. Start carvedilol or Coreg CR (in patients with low BP), at lowest dose as 1st line of therapy
3. If BP allows, start Ramipril (2.5-10 mg/day) or valsartan/sacubitril
4. Start spironolactone (12.5-50 mg/day)
5. Start furosemide for volume control
6. Consider digoxin, hydralazine and nitrates
7. Consider ivabradine for HR control in patients who cannot tolerate high dose carvedilol
8. Repeat echo, BNP and clinical assessment in 1 month to evaluate LV recovery
9. No more anthracyclines unless endomyocardial biopsy shows <1.5 anthracycline cardiotoxicity
Management of cardiotoxicity from VEGF Inhibitors and 5-FU

**VEGF INHIBITORS**

<table>
<thead>
<tr>
<th>Hypertension Grade 1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Continue therapy</td>
</tr>
<tr>
<td>2. Initiate nifedpine XL 30-120 mg/day</td>
</tr>
<tr>
<td>3. Initiate telmisartan/HCTZ 40/12.5-80/25 mg/day (in absence of prior nephrectomy or abnormal creatinine)</td>
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<table>
<thead>
<tr>
<th>Hypertension Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hold therapy</td>
</tr>
<tr>
<td>2. Initiate nifedpine XL 30-120 mg/day</td>
</tr>
<tr>
<td>3. Initiate telmisartan/HCTZ 40/12.5-80/25 mg/day (in absence of prior nephrectomy or abnormal creatinine)</td>
</tr>
<tr>
<td>4. Consider labetolol 200-800 mg 3x/day</td>
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<tr>
<td>5. Re-challenge again on antihypertensive therapy</td>
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</tbody>
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**5-FU**

<table>
<thead>
<tr>
<th>Coronary vasospasm without left ventricular dysfunction or troponinemia</th>
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</thead>
<tbody>
<tr>
<td>1. Stop therapy</td>
</tr>
<tr>
<td>2. Perform heart catheterization +/- revascularization</td>
</tr>
<tr>
<td>3. Initiate nifedipine XL 30-120 mg/day 2 days before and continue 2 days after infusion</td>
</tr>
<tr>
<td>4. Initiate Imdur 30-120 mg/day 2 days before and continue 2 days after infusion</td>
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<tr>
<td>5. Resume 5-FU infusions as outpatient</td>
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<table>
<thead>
<tr>
<th>Coronary vasospasm with left ventricular dysfunction or increased troponins</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stop therapy</td>
</tr>
<tr>
<td>2. Perform heart catheterization +/- revascularization</td>
</tr>
<tr>
<td>3. Admit patient for 5-FU re-challenge</td>
</tr>
<tr>
<td>4. Initiate nifedipine XL 30-120 mg a day 2 days before and continue 2 days after infusion</td>
</tr>
<tr>
<td>5. Initiate intravenous nitroglycerin 12h before and continue 12h following infusion.</td>
</tr>
</tbody>
</table>
**Evaluation of Cancer Survivors**

**History of anthracycline exposure**

**ASYMPTOMATIC**
1. History and physical exam
2. EKG
3. Complete 2D and 3D
4. Echocardiogram with strain
5. BNP, lipid profile

**SYMPTOMATIC**
1. History and physical exam
2. EKG
3. Complete 2D and 3D
4. Echocardiogram with strain
5. Metabolic stress test
6. BNP, lipid profile
7. Consider cardiac MRI,
8. Consider RHC at rest and with exercise
9. Ziopatch/Holter
10. CT angiography of coronaries with heart flow (intermediate suspicion for CAD)
11. Left heart catheterization (high CAD suspicion)

**History of chest radiation**

**ASYMPTOMATIC**
1. History and physical exam
2. EKG
3. Complete 2D and 3D
4. Echocardiogram with strain
5. CT of chest for calcium scoring

**SYMPTOMATIC**
(chest pain, palpitations, syncope, dyspnea, fatigue or decreased exercise capacity)
1. History and physical exam
2. EKG
3. Complete 2D and 3D
4. Echocardiogram with strain
5. Metabolic stress test
6. BNP, lipid profile, TSH
7. CT angiography of coronaries with heart flow (intermediate suspicion for CAD)
8. Left heart catheterization (high suspicion)
9. Consider metabolic stress test
10. Consider rest and exercise right heart catheterization
11. Ziopatch/Holter
Conclusions

• Cardiovascular morbidity can impair outcomes of both cancer patients and survivors

• Field of intense research- clinical, translational and basic

• Targeted cancer therapies potentially shed light on mechanisms of cardiac injury

• Prevention, surveillance and treatment are important for patient outcomes.

• Advanced heart failure therapies may play a major role in cancer survivors with irreversible cardiovascular injuries
Thank You!

Questions?