Cardio-Oncology
Duke Advanced Heart Failure Symposium
Michel G. Khouri, MD
October 5, 2013
Disclosures

• None
Cardio-Oncology

• An emerging field to keep pace with the rapid evolution of cancer therapies and the incidence, magnitude and consequences of their CV side effects

• Relevant to cancer survivorship:
  i. Early CV toxicities arising during treatment may interfere with completion of very therapies needed to enhance survivorship
  ii. CV issues arising after cancer therapy completion

• New frontier in medicine
  • CV toxicities of novel targeted cancer therapies
### Improvements in longevity after cancer

<table>
<thead>
<tr>
<th>Site</th>
<th>1975 (%)</th>
<th>2007 (%)</th>
<th>% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>50</td>
<td>67</td>
<td>17</td>
</tr>
<tr>
<td>Childhood</td>
<td>30</td>
<td>79</td>
<td>49</td>
</tr>
<tr>
<td>Prostate</td>
<td>67</td>
<td>99</td>
<td>32</td>
</tr>
<tr>
<td>Breast</td>
<td>75</td>
<td>90</td>
<td>15</td>
</tr>
<tr>
<td>Colon</td>
<td>51</td>
<td>65</td>
<td>14</td>
</tr>
<tr>
<td>Lung</td>
<td>12</td>
<td>16</td>
<td>4</td>
</tr>
</tbody>
</table>

- Dramatic improvements in early detection and adjuvant therapy → significant survival gains
- ~13m cancer survivors in the US (~25m worldwide)
  - Projected to explode with further improvements
- Increased risk of the late-effects of cancer therapy

American Cancer Society, Surveillance Research 2012
Cancer Therapy and the Heart

Cardiotoxicity

I. Is there a problem?
II. How serious is the problem?
III. Why is there a problem?
IV. What can we do about the problem?
Is there a problem?

Among 63,566 breast cancer patients from Jan 1992 - Dec 2000, CVD was leading cause of death, followed by breast cancer.

Among women who died as a result of CVD, only 25% were also categorized as having CVD as a co-morbid condition at time of breast cancer diagnosis.

Scope of the problem
Anticancer therapies with CV complications

<table>
<thead>
<tr>
<th>Class/drug</th>
<th>Selected indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytostatic chemotherapeutics</td>
<td></td>
</tr>
<tr>
<td>Anthracyclines/analougues</td>
<td>Lymphoma, Leukaemia, Breast cancer, Ovarian cancer, Sarcoma</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
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<tr>
<td>Daunorubicin</td>
<td></td>
</tr>
<tr>
<td>Epirubicin</td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Leukaemia, Multiple sclerosis</td>
</tr>
<tr>
<td>Pyrimidine analogues</td>
<td></td>
</tr>
<tr>
<td>Fluourouracil (5-FU)</td>
<td>Colorectal cancer, Breast cancer</td>
</tr>
<tr>
<td>Capecitabine</td>
<td></td>
</tr>
<tr>
<td>Alkylation agents</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Breast cancer, Genitourinary cancer</td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
</tr>
<tr>
<td>Anti-microtubule agents</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Breast cancer, Colorectal cancer</td>
</tr>
<tr>
<td>Signalling inhibitors</td>
<td></td>
</tr>
<tr>
<td>Anti-HER2</td>
<td>Breast cancer, Gastric cancer</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td></td>
</tr>
<tr>
<td>Angiogenesis inhibitors/anti-VEGF</td>
<td>Gastrointestinal cancer, Renal cell carcinoma, Hepatocellular cancer</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td></td>
</tr>
<tr>
<td>BCR-ABL inhibitors</td>
<td>Leukaemia</td>
</tr>
<tr>
<td>Imatinib</td>
<td></td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Gastric cancer</td>
</tr>
<tr>
<td>Nilotinib</td>
<td></td>
</tr>
</tbody>
</table>

Radiation (cardiac ischemia, valvular disease, pericardial disease, arrhythmia)

Anthracyclines (cardiomyopathy)
Anti-metabolites (SFU) (ischemia, vasospasm)
Her2-targeted therapies (cardiomyopathy)
VSP inhibitors (hypertension, heart failure, thrombosis)

BCR-ABL inhibitors (peripheral vascular disease?)
HDAC inhibitors (arrhythmia?)
Proteasomal inhibitors (cardiomyopathy?)
PI3K inhibitors (hyperglycemia, myocardial disease?)
mTOR inhibitors (metabolic syndrome?)
PARP inhibitors (?)
CDK inhibitors (?)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Target</th>
<th>CA</th>
<th>Heart Failure</th>
<th>↓ LVEF</th>
<th>HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Breast, Lymphoma</td>
<td>5%</td>
<td>19-40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Single-target therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2</td>
<td>Breast</td>
<td>4%</td>
<td>2-27%</td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>HER2</td>
<td>Breast</td>
<td>&lt; 1%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>Solid tumors</td>
<td>2%</td>
<td>3%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Multi-target therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGF, PDGF, etc.</td>
<td>RCC, GIST</td>
<td>4%</td>
<td>28%</td>
<td>47%</td>
</tr>
<tr>
<td>Sorafenib</td>
<td></td>
<td>RCC, HCC</td>
<td>3%</td>
<td>17-43%</td>
<td></td>
</tr>
</tbody>
</table>
How serious is the problem?

Incidence of CV complications - Radiation therapy

- Incidence of CV complications with radiation therapy
- Darby, et al. NEJM 2013

Graph showing:
- Percent Increase in Rate of Major Coronary Events (95% CI)
- Cumulative Risk of Death from Ischemic Heart Disease (%)

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

Mean Dose of Radiation to Heart (Gy)

Age (yr)
Why is there a problem?
The ‘multiple-hit’ hypothesis

- Cytotoxic chemotherapy
- Signaling inhibitors
- Radiation

Direct Effects

Cancer Diagnosis

Decreased Cardiovascular Reserve

Indirect Effects

Aging
Co-morbid conditions (HTN)
Modifiable Lifestyle Risk Factors (deconditioning, obesity)

Cardiotoxicity (↓ LVEF / HF)

↑ Baseline Cardiovascular Risk Factors

Adapted from Jones, et al. J Am Coll Cardiol 2007
Direct Toxicity
Anthracyclines

Anthracycline-Induced Oxidative Stress

- p53
- GATA-4
- CPC
- Calcium Overload
- AMPK

Apoptosis
Protein Synthesis Suppression
Ultrastructural Changes
Energy Metabolism Alteration

Myocardial Dysfunction

Heart Failure

Direct Toxicity
Anti-HER2 Agents

Cardiac Stress
Anthracyclines
Ischemia
Hypertension

↑ Neuregulin-1

Trastuzumab
Pertuzumab

HER1/3/4
HER2 (ErbB2)

Lapatinib

Protein Synthesis
Protein Degradation
Cell Survival
Protein Hypertrophy

Myocardial Dysfunction / Heart Failure

Adapted from Khouri, et al. Circulation 2012
Direct Toxicity
Interplay of Anthracycline and Anti-HER2 Agents

Adapted from Tocchetti, et al. Eur J Heart Fail 2012
Direct Toxicity
Angiogenesis (VSP) Inhibitors

Ischemia Hypertension → HIFα → ↑VEGF → ↑PDGF → Bevacizumab

Sunitinib, Sorafenib, Pazopanib, Axitinib, Vandetanib

PDGFR, C-Kit, VEGFR (1/2/3)

Cell survival
Vasodilation (NO production)
Angiogenesis
Prostaglandin production

Hypertension
Thromboembolism (VTE, ATE)
Myocardial Dysfunction / Heart Failure

Adapted from Khouri, et al. Circulation 2012
Why is there a problem?
Cancer drug development

Small molecule kinase inhibitors

Kinase inhibitors in clinical trials (2011)

Adapted from T. Force

chemspot.com
Summary I

• Advancements in diagnostic tools and therapies have dramatically improved cancer-specific survival
• Adverse cardiac effects of conventional therapies remain
• Newer adjuvant therapies interfere with molecular pathways crucial to normal cardiovascular health
  • Numerous more drugs are in the pipeline
• The cancer survivor population is aging with a higher prevalence of traditional CVD risk factors
• If these current trends continue, further improvements in cancer-specific and overall survival may be offset by increased therapy-associated CV mortality
What can we do about the problem?

Left Ventricular Dysfunction in Patients Receiving Cardiotoxic Cancer Therapies
Are Clinicians Responding Optimally?

Yoon, et al. JACC 2010

Cardioprotection During Chemotherapy
Need for Faster Transfer of Knowledge From Cardiology to Oncology and Role for a Cardio-Oncologist*

Smiseth, et al. JACC 2013
Introduction to Cardiotoxicity Review Series
Thomas Force
What can we do about the problem?

Areas of Investigation / Improvement

I. Defining Cardiotoxicity

II. Detection

III. Prevention / Treatment
## Definitions of Cardiotoxicity

<table>
<thead>
<tr>
<th>Classification System</th>
<th>Low</th>
<th>Severity</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Grade 1 (mild)</td>
<td>Grade 2 (moderate)</td>
</tr>
<tr>
<td>CTCAE, v4.03 Heart failure</td>
<td></td>
<td>Asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities</td>
<td>Symptoms with mild to moderate activity or exertion</td>
</tr>
<tr>
<td>CTCAE, v4.03 EF decline</td>
<td></td>
<td>Resting EF 50-40%; 10-19% ↓ from baseline</td>
<td>Resting EF 39-20%; &gt; 20% ↓ from baseline</td>
</tr>
<tr>
<td>Cardiac Review and Evaluation Committee (CREC)</td>
<td></td>
<td>Any of 4 criteria confirms cardiotoxicity:</td>
<td></td>
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<td></td>
<td></td>
<td>(1) Cardiomyopathy – reduced LVEF (global or more severe in the septum)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>(2) Symptoms of HF</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>(3) Signs associated with HF (S3 gallop and / or tachycardia)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>(4) Decrease in LVEF from baseline ≥ 5% to &lt; 55% with accompanying signs or symptoms of HF, or decline in LVEF ≥10% to &lt; 55% without accompanying signs or symptoms of HF</td>
<td></td>
</tr>
<tr>
<td>Drug continuation: LVEF criteria in clinical trials and practice</td>
<td></td>
<td>(1)&gt; 10% LVEF declines from baseline, to &lt; 55%,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2)≥ 10% LVEF decline from baseline, to &lt; 50%,</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>(3)≥ 20% or &gt; 15% LVEF decline from baseline, but remains ≥ 50%, or</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>(4)Any LVEF decline to &lt; 50%</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Khouri, et al. *Circulation* 2012
Implications of current definitions

• Differing LVEF parameters hinder accurate assessment of the frequency and magnitude of drug-induced LV dysfunction
• Clinical importance of current definitions of cardiotoxicity remains unknown
• Long-term natural history of LVEF during and post-therapy remains unknown
  • What degree of LVEF decline is important?
Detection of Cardiotoxicity

- Resting LVEF = Standard of Care
  - 2D Echo or MUGA
- Limitations of LVEF
  - Insensitive measure of subclinical cardiac injury
    - Compensation masks chemo-induced early myocyte damage
  - Decline evident only once significant damage has occurred
    - Too late to avert irreversible cardiomyopathy
- Limitations of current detection approaches
  - No evidence-based guidelines of timing / frequency
  - Unchanged LVEF often equated to a lack of cardiotoxicity
Detection
New Approaches

Diagnostic testing

Emerging Biomarkers
- Biochemical markers
- Strain echo (tissue Doppler/speckle tracking)
- Cardiac magnetic resonance imaging
- Targeted nuclear cardiology
- Functional capacity testing

Traditional Imaging
- Echocardiography
- Nuclear cardiology

Surveillance

Diagnosis

Guide treatment

Disease Progression

Baseline CV health & Risk factors
Cancer Diagnosis
Cytotoxic Therapy ("CV insult")
Cardiac toxicity (↓LVEF) (ACC/AHA Stage B)
CV disease & Premature death
Heart failure (ACC/AHA Stage C & D)

Early detection
Biochemical markers

Early detection
Novel cardiac imaging – 3-Dimensional Echo LVEF

\[
y = 0.54x + 15.85 \\
r = 0.53
\]

\[
y = 0.92x + 1.61 \\
r = 0.97
\]

\[
y = 0.92x + 1.56 \\
r = 0.97
\]


Thavendiranathan, et al. JACC 2012
Early detection

Novel cardiac imaging – Speckle-tracking Strain Echo

Hare, et al. Am Heart J 2009
Early detection
Novel cardiac imaging – Cardiac MRI

Adverse effects of adjuvant therapy on CV system

- Pulmonary function (Chemotherapy, RT) +
- Cardiac function (DOX, Trastuzumab, RT, anti-VEGF+)
- Vascular compliance (DOX, RT, anti-VEGF) +
- Skeletal muscle function (Decadron, HT, chemo?, anti-VEGF?)

↓↓↓↓ CV reserve

CV late-effects in cancer: Running on empty

Early detection
Cardiopulmonary testing

↓ 5.5 ml.kg.min (31%); p=0.01

<table>
<thead>
<tr>
<th>Cohort</th>
<th>40yrs</th>
<th>50yrs</th>
<th>60yrs</th>
<th>70yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients After Therapy (n=140)</td>
<td>21.05</td>
<td>19.51</td>
<td>17.97</td>
<td>16.44</td>
</tr>
<tr>
<td>Healthy controls (n=107)</td>
<td>29.82</td>
<td>26.32</td>
<td>22.82</td>
<td>19.32</td>
</tr>
</tbody>
</table>

Early detection
Cardiac exercise testing

Resting 2D Echo LVEF

Maximal exercise stress test

Post-Peak SV

VO$_{2peak}$

<table>
<thead>
<tr>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>$55%$</td>
<td>$60%$</td>
</tr>
<tr>
<td>$p=0.37$</td>
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</table>

<table>
<thead>
<tr>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>$30$ mL</td>
<td>$50$ mL</td>
</tr>
<tr>
<td>$p&lt;0.05 \downarrow 8$ mL (13%)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>$25$ mL.kg.min</td>
<td>$30$ mL.kg.min</td>
</tr>
<tr>
<td>$p&lt;0.05 \downarrow 6.5$ mL.kg.min (25%)</td>
<td></td>
</tr>
</tbody>
</table>

Khouri, et al. Submitted 2013
Prevention and Treatment

Diagnostic testing
- Emerging Biomarkers
  - Biochemical markers
  - Strain echo (tissue Doppler/speckle tracking)
  - Cardiac magnetic resonance imaging
  - Targeted nuclear cardiology
  - Functional capacity testing

Surveillance
- Traditional Imaging
  - Echocardiography
  - Nuclear cardiology

Diagnosis
- Cardiac toxicity
  - (↓LVEF) (ACC/AHA Stage B)

Guide treatment
- CV disease & Premature death
  - Heart failure
    - (ACC/AHA Stage C & D)

Disease Progression
- Baseline CV health & Risk factors
- Cancer Diagnosis
- Cytotoxic Therapy ("CV insult")

Prevention and Treatment
- Primordial prevention
- Primary prevention
- Secondary prevention
- Treatment
  - ACE inhibitors
  - Beta blockers
  - Angiotensin Receptor Blockers
  - Statins
  - Exercise

Primordial Prevention

Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy

Nihat Kalay, MD,* Emrullah Basar, MD,* Ibrahim Ozdogru, MD,* Ozlem Er, MD,† Yakup Cetinkaya, MD,* Ali Dogan, MD,* Tugrul Inanc, MD, Abdurrahman Oguzhan, MD,* Namik Kemal Eryol, MD,* Ramazan Topsakal, MD,* Ali Ergin, MD*

Kayseri, Turkey

Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

The OVERCOME Trial (prevention of left Ventricular

<table>
<thead>
<tr>
<th></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>
</tbody>
</table>
Primordial Prevention

Effect of Statin Therapy on the Risk for Incident Heart Failure in Patients With Breast Cancer Receiving Anthracycline Chemotherapy

An Observational Clinical Cohort Study

Sinziana Seicean, MD, MPH, PhD,*,† Andreea Seicean, MPH,† Juan Carlos Plana, MD,† G. Thomas Budd, MD,† Thomas H. Marwick, MD, PhD, MPH*‡

p=0.03

Primary Prevention

Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

Daniela Cardinale, MD; Alessandro Colombo, MD; Maria T. Sandri, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Maurizio Civelli, MD; Giovanni Martinelli, MD; Fabrizio Veglia, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

Controls

ACEI-group

with (•) or without (□) persistent Tnl increase

Secondary Prevention

CONSIDERED EVENTS:
- Sudden death
- Cardiac death
- Acute pulmonary edema
- Heart failure
- Life-threatening arrhythmias
- PM implantation

Cardinale, et al. J Am Coll Cardiol 2010
Symptomatic Heart Failure

Treatment of Cancer-Therapy Induced Heart Failure
Clinical Studies: 1973 - Present

<table>
<thead>
<tr>
<th>Therapy</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digitalis + Diuretics</td>
<td>46</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>21</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>6</td>
</tr>
<tr>
<td>ACE Inhibitors + Beta Blockers</td>
<td>39</td>
</tr>
<tr>
<td><strong>Total patients</strong></td>
<td><strong>112</strong></td>
</tr>
</tbody>
</table>
Summary II

• Lack of a universal definition of cardiotoxicity
  • Limits understanding of true incidence
• Detection
  • Troponin (I, T, hs) has promising predictive abilities
    • Small trials and variable timing of assessments limit application
  • Strain and strain rate imaging may detect subclinical cardiac dysfunction
    • Predictive value remains uncertain
  • Abnormal cardiorespiratory fitness may be early mortality risk predictor
    • CPET may be limited by availability
• Treatment / Prevention
  • Current state of the art therapies – ACE inhibitors and Beta blockers
  • Evidence limited in CA patients; based mostly on general HF guidelines
  • Optimal timing and duration of medical therapies uncertain
  • Studies ongoing to evaluate exercise as intervention
### Clinical Cardio-Onc at DUMC

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Prior to Therapy</th>
<th>After Therapy Initiation</th>
<th>Adverse Event</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSP inhibitors</td>
<td>Aggressive BP management (JNC 7 guidelines)</td>
<td>Weekly BP checks (6 weeks)</td>
<td>Hypertension</td>
<td>Aggressive BP control:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1) ACE-I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2) Dihydropyridine CCB’s</td>
</tr>
<tr>
<td></td>
<td>UA for proteinuria</td>
<td>UA for proteinuria</td>
<td></td>
<td>Titration of BP meds during chemo “holidays”</td>
</tr>
<tr>
<td></td>
<td>Ensure no active angina/symptomatic CAD</td>
<td>Ensure no active angina or symptomatic CAD</td>
<td>MI; CVA</td>
<td>Stop VSP inhibitor</td>
</tr>
<tr>
<td></td>
<td>Initiate anti-platelet therapy for prior CAD or PAD</td>
<td></td>
<td></td>
<td>Start guideline based management</td>
</tr>
<tr>
<td></td>
<td>Baseline 2D TTE +/-:</td>
<td>Repeat TTE (as necessary) for signs/symptoms of LVSD</td>
<td>LVSD; HF</td>
<td>Stop VSP inhibitor</td>
</tr>
<tr>
<td></td>
<td>3D LVEF Strain</td>
<td></td>
<td></td>
<td>Start ACE-I + B-BI</td>
</tr>
<tr>
<td></td>
<td>Aggressive management of cardiac risk factors (especially HTN)</td>
<td>Repeat TTE (as necessary) for signs/symptoms of LVSD</td>
<td>LVSD; HF</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Baseline 2D TTE +/-:</td>
<td>Consider Troponin evaluation at each cycle during therapy</td>
<td>Troponin (+)</td>
<td>ACE-I</td>
</tr>
<tr>
<td></td>
<td>3D LVEF Strain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aggressive management of cardiac risk factors (especially HTN)</td>
<td>TTE at end of chemo</td>
<td>LVSD; HF</td>
<td>ACE-I + B-BI</td>
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<td>TTE Q3 months for 1st year; TTE annually</td>
<td>LVSD; HF</td>
<td></td>
<td>ACE-I + B-BI</td>
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<tr>
<td>Trastuzumab</td>
<td>Baseline 2D TTE +/-:</td>
<td>TTE Q3 months for 1st year</td>
<td>LVSD; HF</td>
<td>Hold Trastuzumab for 1 month</td>
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<tr>
<td></td>
<td>3D LVEF Strain</td>
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<td>Start ACE-I + B-BI</td>
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<tr>
<td></td>
<td>Aggressive management of cardiac risk factors (especially HTN)</td>
<td>LVEF, HF normalized</td>
<td>Resume Trastuzumab</td>
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<td>Continue ACE-I + B-BI</td>
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<tr>
<td></td>
<td></td>
<td>LVEF, HF remains</td>
<td>Continue holding Trastuzumab</td>
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<td></td>
<td>Intensify ACE-I + B-BI</td>
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<td></td>
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<td></td>
<td>Re-measure LVEF after “holiday”</td>
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<td></td>
<td></td>
<td>Persistent LVSD; HF</td>
<td>Stop Trastuzumab</td>
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<td>Individualize decision if Trastuzumab only option</td>
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<tr>
<td></td>
<td>Post-completion</td>
<td>Normal LVEF; no HF</td>
<td>No cardiac monitoring</td>
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<tr>
<td></td>
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<td>LVSD; HF</td>
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