Cardio-oncology: Basics and Knowing When You Need an Echo

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No Disclosures

• Acknowledgement: Nausheen Akhter, MD, Director of the cardio-oncology program at Northwestern
Introduction

• The number of cancer therapies have significantly increased
• Cancer survival has improved
• A number of cancer therapies have cardiotoxic effects

Cardiotoxic Syndromes Associated with Chemo

Agents associated with LV dysfunction
• Anthracylines
• Mitoxanthrone
• Cyclophosphamide
• Trastuzumab
• Ifosfamide
• All-trans retinoic acid

Agents associated with ischemia
• 5-FU
• Cisplatin
• Capecitabine (Xeloda)
• IL-2

Agents associated with hypertension
• Bevacizumab (Avastin)
• Cisplatin
• IL-2

Agents associated with Other toxic effects
• Tamponade or endomyocardial fibrosis (Busulfan)
• Hemorrhagic Myocarditis (Cyclophosphamide)
• Bradycardia (Taxol, Thalidomide)
• Raynaud’s (Vinblastine)
• Autonomic neurop (Vincristine)
• Long QT (Arsenic trioxide)
• Pulm fibrosis (Bleo)

Yeh et al. Circulation 2004
Angiogenesis Inhibitors

- Angiogenesis is a key factor for tumor growth and survival.
- Angiogenesis inhibitors have shown to improve outcomes in various malignancies.
- Tumor growth suppression achieved by:
  - Direct inhibition of VEGF ligand’s ability to target receptor (bevacizumab, ramucirumab, aflibercept)
  - Small molecules that inhibit tyrosine kinases (sunitinib, sorafenib, pazopanib, vandetanib, vatalanib, cobazantinib, axitinib, regorafenib)

Odds ratio for adverse cardiac events due to angiogenesis inhibitors

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Odds Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial thromboembolism</td>
<td>1.52 [1.17, 1.98]</td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>1.35 [1.06, 1.70]</td>
</tr>
<tr>
<td>Cardiac ischemia</td>
<td>2.83 [1.72, 4.65]</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>1.66 [0.84, 3.30]</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.20 [0.86, 1.66]</td>
</tr>
<tr>
<td>Fatal cardiovascular events</td>
<td>1.26 [0.63, 2.53]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.28 [4.53, 6.15]</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.94 [0.58, 1.52]</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>5.59 [4.67, 6.69]</td>
</tr>
<tr>
<td>Unspecified thromboembolism</td>
<td>1.28 [0.95, 1.73]</td>
</tr>
<tr>
<td>Unspecified venous thromboembolism</td>
<td>1.07 [0.97, 1.19]</td>
</tr>
</tbody>
</table>


EXPERT CONSENSUS STATEMENT

Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

Juan Carlos Plana, MD, FASE, Chair, Maurizio Galderisi, MD, FESC, Co-Chair, Ana Barac, MD, PhD, Michael S. Ewer, MD, JD, Bonnie Ky, MD, FASE, Marie Scherer-Crosbie, MD, PhD, FASE, Javier Gannane, MD, PhD, FASE, Igal A. Sebag, MD, FASE, Deborah A. Agler, RCT, RDMS, FASE, Luigi P. Badano, MD, PhD, FESC, Jose Banchs, MD, FASE, Daniela Cardinale, MD, PhD, FESC, Joseph Carver, MD, Manuel Cernqueira, MD, Jeanne M. DeCara, MD, FASE, Thor Edvardsen, MD, PhD, FESC, Scott D. Flihm, MD, MBA, Thomas Force, MD, Brian P. Griffin, MD, Guy Jerusalem, MD, PhD, Jennifer E. Liu, MD, FASE, Andrea Magalhaes, MD, Thomas Marwick, MBBS, PhD, MPH, Liza Y. Sanchez, RCS, FASE, Rosa Sicari, MD, PhD, FESC, Hector R. Villaragga, MD, FASE, and Patrizio Lancellotti, MD, PhD, FESC, Cleveland, Ohio; Naples, Padua, Milan, and Pisa, Italy; Washington, District of Columbia; Houston, Texas; Philadelphia, Pennsylvania; Boston, Massachusetts; Hamilton, Ontario and Montreal, Quebec; Canada; Chicago, Illinois; Oslo, Norway; Liege, Belgium; New York, New York; Lisbon, Portugal; Hobart, Australia; Rochester, Minnesota

CTRCD Defined

- CTRCD (Cancer Therapeutics-Related Cardiac Dysfunction)
  - Decrease in LVEF > 10% to a value < 53%

Reversible: to within 5% points of baseline

Partially reversible: improved by >10% points from the nadir but remaining >5% points below baseline

Irreversible: improved by < 10% points from the nadir and remaining > 5% points below baseline

Plana, JC et al. JASE 2014; 27: 911-39

CTRCD

<table>
<thead>
<tr>
<th>TYPE 1</th>
<th>TYPE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anthracycline-induced</td>
<td>• Non-ANT agents</td>
</tr>
<tr>
<td>• Dose-related</td>
<td>• Not dose related</td>
</tr>
<tr>
<td>• Irreversible damage</td>
<td>• Generally reversible</td>
</tr>
<tr>
<td>• Early treatment with HF</td>
<td>myocardial dysfunction</td>
</tr>
<tr>
<td>therapy can prevent LV</td>
<td>No apparent ultrastructural</td>
</tr>
<tr>
<td>remodeling/EF decline</td>
<td>abnormalities</td>
</tr>
</tbody>
</table>

Plana, JC et al. JASE 2014; 27: 911-39
### Type 1 CTRCD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxic Dose Range</th>
<th>Cardiac Toxicity</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>&gt;450 mg/m2</td>
<td>LVD</td>
<td>3–12%</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>&gt;720 mg/m2</td>
<td>LVD</td>
<td>0.9–3.3%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Conventional dose</td>
<td>LVD</td>
<td>5–15%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td></td>
<td>HF</td>
<td>2–8%</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>&gt;150 mg/kg</td>
<td>HF 1-10d after 1st dose</td>
<td>7-28%</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td></td>
<td>HF</td>
<td>10-30%</td>
</tr>
</tbody>
</table>

Oreto et al. JASE 2012


### Type 2 CTRCD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cardiac Toxicity</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>LVD With concurrent anthracycline</td>
<td>2–10% 27%</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Asymptomatic cardiac events, reversible LVD</td>
<td>1%</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>LVD Hypotension</td>
<td>10-30%</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>LVD</td>
<td>2-3%</td>
</tr>
</tbody>
</table>

Which echo measures can you use to predict CTRCD?

LV EF (2D/3D)
Diastology
Tissue Doppler Imaging ($s'$)
MAPSE
Myocardial Deformation Imaging

Strain Imaging

Strain = % change in length of the myocardium during relaxation and contraction

\[
\text{Strain} = \frac{L_B - L_A}{L_A} = \frac{\Delta L}{L_A}
\]

$L_A = \text{Myocardial length at end diastole}$
$L_B = \text{Myocardial length at end systole}$

Courtesy of Ben Freed, MD
Anthracyclines

• Cardiac damage thought to occur by:
  – Production of free radicals
  – Free radicals are highly toxic and react with lipids, proteins and nucleic acids
  – Results in lipid peroxidation, depletion of sulfhydryl-containing peptides, and damage to DNA.
  – Cardiac myocytes have low levels of free radical scavenging systems

Anthracycline Toxicity: Acute, Subacute, Chronic

• Acute – 1st week of therapy
  – < 1% of pts immediately after infusion
  – Transient, reversible decrease in LVEF
  – Improves with discontinuation

• Subacute onset – 1st year of therapy
  – 1.6 % to 2.1 % of patients
  – Dose-related decrease in LVEF, irreversible
  – Can progress to clinical HF

• Chronic or late onset > 1 year after therapy
  – 1.6 % to 5% of patients
  – Can be triggered by a secondary insult, generally irreversible

Dose-related ANT Toxicity


Anthracycline Cardiotoxicity: Risk Factors

- Cumulative dose
- Method of administration: IV bolus administration, higher single dose, dose dense therapy
- Baseline low EF
- Older age
- Prior or concomitant RT
- Concomitant cardiotoxic chemotherapy
  - Trastuzumab

48 yo M with h/o LCX infarct diagnosed with DLBCL who presents for baseline echo prior to undergoing doxorubicin-based chemotherapy.

Baseline EF = 49%

Baseline Bull’s Eye with LCX infarct, GLS: -13.9%
48 yo M with h/o LCX infarct and DLBCL s/p CHOP chemotherapy (total doxorubicin dose 300 mg/m²) presents for post-chemo echo.

Post Chemo EF = 33%

48 yo M with h/o LCX infarct and DLBCL s/p CHOP chemotherapy (total doxorubicin dose 300 mg/m²) presents for post-chemo echo.

Post Chemo GLS: - 9.6%
Pre-CHOP Chemotherapy

Baseline

EF = 49%
GLS = -13.9%

Post CHOP Chemotherapy

Baseline

EF = 33%
GLS = -9.6%

Integrated Approach

Initiation of regimen potentially associated with Type 1 toxicity

Baseline LVEF (3DE/2DE)
GLS, Troponin I

LVEF < 53%
GLS < LLN
- Troponin

Cardiology consult

LVEF > 53%
GLS > LLN
+ Troponin

FU at completion of therapy and 6 months later

Plana, JC et al. JASE 2014; 27: 911-39
25 yo male with newly dx AML s/p 7+3 chemotherapy, septic in ICU, had a normal baseline echo.

10 days later
3 weeks later

**Trastuzumab**

- Human epithelial growth factor 2 (HER-2) is over expressed in approx 20% breast cancer pts
- Amplifications of HER-2 associated with decreased survival and increased recurrence
- Trastuzumab (Herceptin) is a humanized HER-2 monoclonal antibody FDA approved in 1998
Trastuzumab Cardiac Toxicity

- Mechanism not fully understood
- Directly related to HER-2 receptor blockade
- HER-2 receptors expressed on myocytes for protection from cardiotoxins and for embryonic cardiac development.
- Inhibition of HER-2 receptor blocks ErbB2 signaling that is responsible for growth, repair and survival of myocytes
- Suppression of HER-2 gene in mice resulted in DCM
### Herceptin Adjuvant Trial (HERA): Cardiac Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Trastuzumab (n = 1,678)</th>
<th>Observation (n = 1,708)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>0 (0%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Severe CHF (not including cardiac death)</td>
<td>10 (0.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Symptomatic CHF (including severe CHF, not including cardiac death)</td>
<td>36 (2.15%)</td>
<td>2 (0.12%)</td>
</tr>
<tr>
<td>Confirmed significant LVEF drop (asymptomatic or mildly symptomatic)</td>
<td>51 (3.04%)</td>
<td>9 (0.53%)</td>
</tr>
<tr>
<td>Any type of cardiac end point (at least one occurrence of cardiac adverse events above)</td>
<td>61 (3.64%)</td>
<td>10 (0.59%)</td>
</tr>
<tr>
<td>At least one significant LVEF drop</td>
<td>118 (7.03%)</td>
<td>35 (2.05%)</td>
</tr>
</tbody>
</table>


### Cardiac Monitoring Based on Initial Trastuzumab Trials

- LVEF at baseline, following completion of chemo (usually Adria, Cyclophos)
- LVEF at 3, 6, +/-9, 12, 18 months from initiation of chemo
- Metastatic disease: Infrequent monitoring in absence of symptoms
Trending Strain For Prognostication

- 81 women with HER 2+ disease were prospectively studied, 37 who had also received concurrent ANT.

- 30% of patient had a decrease in GLS at 6 months who later developed cardiotoxicity.

- Strongest predictor of cardiotoxicity was change in GLS of 11%, sensitivity 65% specificity 94%.

- Compared to baseline strain measurements, “reductions of strain of <8% appear not to be meaningful, and those >15% are very likely to be abnormal.”


Plana, JC et al. JASE 2014; 27: 911-39

Integrated Approach

Initiation of trastuzumab

Baseline LVEF (3DE/2DE)
GLS, Troponin I

LVEF < 53%
GLS < LLN
+ Troponin
Cardiology consult

LVEF > 53%
GLS > LLN
- Troponin
FU every 3 months on therapy

Ptana, JC et al. JASE 2014; 27: 911-39
Initiation of trastuzumab after regimen associated with Type 1 toxicity

Baseline LVEF (3DE/2DE)
GLS, Troponin I

LVEF < 53%
GLS < LLN
+ Troponin
Cardiology consult

LVEF > 53%
GLS > LLN
- Troponin
FU every 3 months on therapy and 6 months later

Drop of 10 points to LVEF < 53%

Relative drop of GLS as Compared to baseline

<8%
No evidence of subclinical LV dysfunction

>15%
Subclinical LV dysfunction

Yes → CTRCD

Plana, JC et al. JASE 2014; 27: 911-39
55 yo female with HTN, HER2 + breast cancer s/p AC-TH, on maintenance trastuzumab.

Baseline echo, EF 60%, GLS -21%

55 yo female with HTN, HER2 + breast cancer s/p AC-TH, on maintenance trastuzumab. 3 month surveillance echo...

3 month echo, EF 54%, GLS -16%
55 yo female with HTN, HER2 + breast cancer s/p AC-TH, on maintenance trastuzumab. 6 month surveillance echo...

Late Cardiac Effects

- Anthracyclines can manifest cardiotoxicity late in life, especially when used in pediatric pts
- Risk of adverse effects of chest radiation increases with time
Sites of Cardiac Involvement

- Coronary Artery Disease
- Myocardial Dysfunction
- Pericardial Disease
- Conduction Abnormalities
- Valvular Heart Disease

EACVI/ASE Recommended Algorithm for Patient Management Following XRT

J Am Soc Echocardiogr 2013;26:1013-32
Summary

• Variety of cancer drugs are now available and have improved cancer survival
• Several agents have cardiotoxic effects
• Echo is the primary imaging modality to follow patients at baseline, during treatment and long term
• Toxicity is agent-specific. Imaging and clinical followup is specific to the disease and agents used for treatment

Thank You