Guideline-Driven Care in Cardio-Oncology: Utilizing Recommendations Across Disciplines

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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

- Summarize the key points
- Science behind the recommendations
- Apply the document to clinical practice
- Take home messages

(J Am Soc Echocardiogr 2014;27:911-39.)

Keywords: Chemotherapy, Doxorubicin, Trastuzumab, Left ventricular dysfunction, Three-dimensional echocardiography, Early detection, Strain, Biomarkers
I. CTRCD – definition, classification and mechanisms of toxicity
II. Echocardiographic evaluation of the patient undergoing cancer therapy
III. Early detection of toxicity
IV. Other imaging modalities
V. Integrated approach

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
I. CTRCD – definition, classification and mechanisms of toxicity
Forms of Cardiotoxicity

• LV dysfunction
  – *Cancer therapeutics-related cardiac dysfunction or CTRCD*

• Ischemia

• HTN

• Arrhythmia

• Thromboembolism

• QT prolongation
I. Cancer Therapeutics-Related Cardiac Dysfunction (CTRCD)

• Definition
  – A decline in EF from baseline of >10% to a value <53%

• Symptomatic or asymptomatic

• Reversible or irreversible

• Type 1 or Type 2
Classification of CTRCD
Type 1 vs. Type 2

- Cancer
  - Cancer Therapeutics
    - Regimen potentially associated with Type I toxicity
      - Doxorubicin
      - Epirubicin
      - Idarubicin
      - Mitoxantrone
    - Regimen potentially associated with Type II toxicity
      - Trastuzumab
      - Lapatinib
      - Pertuzumab
      - Imatinib
      - Sorafenib
      - Sunitinib
      - Bevacizumab
      - Bortezomib
Consensus Statement: Differentiation of CTRCD into Type 1 and Type 2

Type I CTRCD
• Prototype: doxorubicin
  – Cumulative dose-dependent
  – Irreversible damage
  – Cellular apoptosis/necrosis
  – Ultrastructural changes on biopsy

Type II CTRCD
• Prototype: trastuzumab
  – Not cumulative dose dependent
  – mostly reversible LV dysfunction
  – Cellular dysfunction
  – No biopsy changes
II. Echocardiographic Evaluation of Cardiac Structure and Function in Cancer Patients

LVEF Measurement
Consensus Statement: EF determination
3D LVEF preferred; 2D EF biplane MOD (consider contrast)

- Min change in EF not attributable to measurement variability
  - 2D EF: 10%
  - 3D EF: 6%

- Definition of CTRCD
  - EF reduction from baseline >10% to a value <53%
EF Determination: 3D Echo

• Advantages:
  – More accurate and reproducible than 2D
  – No geometric assumptions
  – Minimize foreshortening
  – Semi-automated border detection

• Disadvantages:
  – Dependent on image quality
  – Learning curve; experience with image acquisition and analysis
  – Availability with equipment and expertise*

Walker et al, JCO 2010
Consensus Statement
EF at baseline and during therapy

Prognostic value of LVEF
LVEF Monitoring: Is it useful?

Table 2. Risk Factors for Trastuzumab/Chemotherapy-Induced Cardiac Events in NSABP B-31

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No. of Patients</th>
<th>No.</th>
<th>%</th>
<th>P</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHF</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline LVEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65%</td>
<td>423</td>
<td>9</td>
<td>2.1</td>
<td>&lt;.001</td>
<td>6.72</td>
<td>2.67 to 16.92</td>
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<tr>
<td>55%-64%</td>
<td>451</td>
<td>19</td>
<td>4.2</td>
<td>.092</td>
<td>1.98</td>
<td>0.89 to 4.37</td>
</tr>
<tr>
<td>50%-54%</td>
<td>70</td>
<td>9</td>
<td>12.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-AC LVEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65%</td>
<td>381</td>
<td>4</td>
<td>1.1</td>
<td>.020</td>
<td>3.58</td>
<td>1.22 to 10.52</td>
</tr>
<tr>
<td>55%-64%</td>
<td>473</td>
<td>19</td>
<td>4.0</td>
<td></td>
<td>11.84</td>
<td>3.90 to 35.99</td>
</tr>
<tr>
<td>50%-54%</td>
<td>111</td>
<td>14</td>
<td>12.6</td>
<td></td>
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</tbody>
</table>

Figure 1. Survival estimates of cardiac event-free survival function according to the baseline LVEF. *p <0.01, ***p <0.0001.

Romond JCO 2012

Scherrer-Crobsie AJC 2015
III. Detection of Subclinical LV Dysfunction

- Imaging
  - Global longitudinal strain (GLS) with 2D echo

- Serum cardiac biomarkers
  - Troponin
Use of Myocardial Strain Imaging by Echocardiography for the Early Detection of Cardiotoxicity in Patients During and After Cancer Chemotherapy

A Systematic Review

Paaladinesh Thavendiranathan, MD,*† Frédéric Poulin, MD,* Ki-Dong Lim, MD,* Juan Carlos Plana, MD,‡ Anna Woo, MD,* Thomas H. Marwick, MD.§

Toronto, Ontario, Canada; Cleveland, Ohio; and Hobart, Australia

Early reduction in GLS predicts subsequent cardiotoxicity

GLS -20.1%
GLS -17.0%
GLS -16.1%

Pre-therapy EF 61%
6M EF 55%
12M EF 49%
Consensus Statement:
• Decrease GLS >15%, subclinical LV dysfunction likely
• Decrease <8%, no evidence of subclinical LV dysfunction

81 BC patients w/ trastuzumab +/- AC

Negichi K, Marwick T JASE 2013

- Decrease of 11% predictive
  95% CI (8.3% - 14.6%)
Prognostic value of biomarkers: troponin

703 pts receiving high dose chemotherapy

*Cardinale D, Circ 2002*

78 BC pts receiving AC + Trastuzuamb

*Ky B, J Am Coll Cardiol 2014*
IV Other Imaging Modalities

- MUGA
- Cardiac MRI

Consensus Statement:
Important to keep imaging modality consistent for baseline and follow-up studies.
V. Integrated Approach

Cardiotoxicity Detection

- EF
- GLS
- Troponin
Baseline Assessment and Monitoring

Type I Agents

Type II agents

* Consider confirmation with CMR.
** LLN = Lower limit of normal. Please refer to Table 5 for normal GLS values based on vendor, gender and age.
*** If the dose is higher than 240 mg/m² (or its equivalent), recommend measurement of LVEF, GLS and troponin prior to each additional 50 mg/m².
Case

• 57 year old woman with HTN, DM and hyperlipidemia
• Breast cancer with high grade invasive ductal CA, ER/PR (-) HER2 (+)
• Recommended treatment:
  – Mastectomy
  – Adriamycin, Cytoxan, Taxol
  – Trastuzumab (1 year treatment)
  – Radiotherapy
Case Study

Baseline EF 63%

Baseline GLS -22.6%
Case Study

Baseline EF 63%
Baseline GLS -22.6%

Post AC, pre-trastuzumab
EF 54%

Post AC, pre-trastuzumab
GLS -17%
What to do?
Algorithm for Adjudicating CTRCD

Baseline 64%
3 mos EF 54%
= EF drop 9%
3 Month f/u

GLS -22.6%
Baseline

GLS = -17.0%
3 months

Δ GLS = 22.6-17.0/22.6 =25%
What to do?
Algorithm for Adjudicating CTRCD

Baseline 64%
3 mos EF 54% = EF drop 9%

Δ GLS = 22.6-17.0/22.6 = 25%
Management of Heart Failure
ACCF/AHA Guideline

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
  - Elderly
  - Family history of cardiomyopathy
  - Using cardiacs

STAGE B
Structural heart disease but without signs or symptoms of HF
- e.g., Patients with:
  - Prior MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

At Risk for Heart Failure

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

At Risk for Heart Failure

STAGE D
Refractory HF
- e.g., Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

Heart Failure

Abnl GLS Troponin??

THERAPY

STAGE A
- Goals:
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities

STAGE B
- Drugs:
  - ACEi or ARB in appropriate patients for vascular disease or DM
  - Stains as appropriate

STAGE C
- Goals:
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality

STAGE D
- Goals:
  - Control symptoms
  - Improve HRQOL
  - Reduce hospital readmissions
  - Establish patients end-of-life goals

THERAPY

HFpEF

- Drugs:
  - ACEi or ARB as appropriate
  - Beta blockers as appropriate
  - In selected patients:
    - ICD
    - Revascularization or revascular surgery as appropriate

HFef

- Drugs:
  - ACEi or ARB
  - Beta blockers
  - Angiotensin antagonists

- Drugs for use in selected patients:
  - Hydration/inotropic/vasodilators
  - ICD and ARB

- In selected patients:
  - CRT
  - ICD
  - Revascularization or revascular surgery as appropriate

- Strategies:
  - Identification of comorbidities

THERAPY

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  - CRT
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  - Revascularization or revascular surgery as appropriate

- Strategies:
  - Identification of comorbidities
What to do?
Adjudication of CTRCD

Consensus Statement:

* The data supporting the initiation of cardioprotection for the treatment of subclinical LV dysfunction is limited.
Take Home Messages

• Two categories of CTRCD: Type 1 exemplified by doxorubicin and Type 2 exemplified by trastuzumab.
• Cardiotoxicity or CTRCD is defined as a drop in EF >10% from baseline to a value <53%.
• LVEF measurement at baseline, during and after therapy:
  – 3D echo preferred or 2D Biplane MOD +/- contrast
  – Keep imaging modality consistent in follow-up
• Strategy of early detection of cardiotoxicity with GLS and/or troponin
• Cardiology consultation recommended for abnormal echo or troponin
• Cooperation between cardiologists and oncologists is absolutely essential.
Thank You

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