Cardiac Toxicity in Breast Cancer Patients

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Disclosures

- I **do intend** to discuss an off-label use of a product during this activity.
- I **have not had** any relevant financial relations during the past 12 months to disclose.
Breast Cancer Therapy and the Heart

Cardiac Toxicity

I. Epidemiology
II. Mechanisms of cardiac/cardiovascular injury
III. Defining cardiac toxicity
IV. Detection of cardiac toxicity
V. Prevention/treatment of cardiac toxicity
Epidemiology of Cardiac Toxicity

- Cardio-toxic drug or treatment in expected long term survivors
  - Dose, location dependent
- Many aspects of CV system may be affected
- A range of severity (and reversibility?)
  - Subclinical
  - Symptomatic
  - Events
- Multiple factors in play
  - Pre-existing CV risk factors/disease
  - Impaired CV reserve
  - Additive insults or ‘Multiple Hit’
- Serious implications
  - Limited access to life saving treatments
  - Long term reductions in quality/quantity of life
Why Worry About Cardiac Toxicity in Breast Cancer?

- Improved detection and therapy → survival gains
- Millions of cancer survivors in the US ... and ↑ in ing
- Acute toxicity can affect access to life saving drugs
- Chronic toxicity can affect survival, morbidity and QOL
Incidence of CVD by Anthracycline Dose

- Congestive heart failure
  - No anthracycline
  - <250 mg/m² anthracycline
  - ≥250 mg/m² anthracycline

- Pericardial disease
- Valvular disease

BMJ 2009; 339: b4606
Incidence of CVD by Radiation Dose

For Congestive heart failure:
- No cardiac radiation
- <500 cGy cardiac radiation
- 500 to <1500 cGy cardiac radiation
- 1500 to <3500 cGy cardiac radiation
- ≥3500 cGy cardiac radiation

For Myocardial infarction:

For Pericardial disease:

For Valvular disease:

Graphs show the cumulative incidence of CVD over time since diagnosis for different radiation dose categories.
Coronary Events in Breast Cancer
Radiation Therapy

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

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

At least one risk factor
No cardiac risk factor

Age (yr)

Darby, et al. NEJM 2013
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

HER1/3/4

HER2 (ErbB2)

Trastuzumab
Pertuzumab

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
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

The ‘multiple hit’ hypothesis

Cytotoxic chemotherapy
Signaling inhibitors
Radiation

Direct Effects

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

Indirect Effects

Baseline Cardiovascular Risk Factors
Cancer Diagnosis
Decreased Cardiovascular Reserve
Cardiotoxicity (↓ LVEF / HF)

Adapted from Jones, et al. J Am Coll Cardiol 2007
CV late-effects in breast cancer

Running on empty

Asymptomatic Maladaptation
Overt Clinical Dysfunction
Chronic Morbidity/Mortality

Normal age-related decline

Cancer

Integrated Concept of Cardiac Toxicity

Disease Progression:
- Baseline CV health & Risk factors
- Cancer Diagnosis
- Cytotoxic Therapy ("CV insult")
- Cardiac toxicity (↓LVEF) (ACC/AHA Stage B)
- CV disease & Premature death

CV reserve ➔ Multiple hit ➔ Subclinical dysfunction ➔ Clinical disease ➔ Heart failure (ACC/AHA Stage C & D)

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

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

Yoon, et al. JACC 2010
Smiseth, et al. JACC 2013
Introduction to Cardiotoxicity Review Series
Thomas Force
What can we do about cardiac toxicity?

Areas of Investigation / Improvement

I. Defining cardiac toxicity
II. Detection
III. Prevention / Treatment
### Definitions of Cardiac Toxicity

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

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 Cardiac Toxicity

• 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

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
- Echocardiography
- Nuclear cardiology

Diagnosis
- Cytotoxic Therapy ("CV insult")
- Cardiac toxicity (↓LVEF) (ACC/AHA Stage B)

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

Baseline CV health & Risk factors

Cancer Diagnosis

Disease Progression

Early detection
Biochemical markers - Troponin

Early detection
Novel cardiac imaging – 3-Dimensional Echo LVEF


Early detection

Novel cardiac imaging – Speckle-tracking Strain Echo

Strain = \frac{\Delta \text{Length}}{\text{Length}_0}

% Thickening

% Thinning

Frame 1  Frame 1 + n

Early detection
Strain Echo vs. Resting LVEF

Hare, et al. Am Heart J 2009
Early detection

Novel cardiac imaging – Cardiac MRI

Early detection of Breast cancer using Cardiopulmonary Exercise Testing.

**Table:**

<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>

*Jones, et al. J Clin Oncol 2012*
Early detection

Resting LVEF vs. Cardiac exercise testing

Resting 2D Echo LVEF

Maximal exercise stress test

Post-Peak SV

p<0.05 ↓ 8 mL (13%)

VO$_2$peak

p<0.05 ↓ 6.5 mL.kg.min (25%)

Patients

Controls

Prevention and Treatment

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

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

Diagnostic testing

Surveillance
- Primary prevention

Diagnosis
- Primordial prevention
- Secondary prevention

Guide treatment
- Prevention and Treatment
  - ACE inhibitors
  - Beta blockers
  - Angiotensin Receptor Blockers
  - Statins
  - Exercise

Heart failure (ACC/AHA Stage C & D)

For effective cardioprotection, timing is the key . . .
Primary Cardioprotection

Assessment & Optimization of risk +/- extent of CV Disease

- Age
- Co-morbid conditions (CAD, HTN, HLP)
- Modifiable lifestyle risk factors (deconditioning, obesity)

Primordial Prevention

Treat all high cardiac risk patients

**Advantages**
- Minimize screening

**Disadvantages**
- Treatment despite:
  - Normal function
  - Low (~5%) overall incidence of overt HF

Primary Prevention

Screen for subclinical dysfunction
(Imaging, blood biomarkers)

**Advantages**
- Minimize unnecessary treatment

**Disadvantages**
- Intensive / frequent screening
- Optimal screening method uncertain
- Potential delayed diagnosis / treatment

**Advantages**
- Early intervention → Limit development of cardiotoxicity

**Disadvantages**
- Duration of treatment uncertain
What is the optimal strategy?

ACC/AHA Heart Failure guidelines (2013)
Stage A: Recommendations (Class I, LOE C)
Conditions that may lead to or contribute to HF, such as ... cardiotoxic agents, should be controlled or avoided.

• “...it may be reasonable to evaluate those who are receiving (or who have received) cardiotoxic chemotherapy agents for LV dysfunction.”
• “The use of advanced echocardiographic techniques or biomarkers to identify increased HF risk in those receiving may be useful …”

ESMO guidelines (2012)
• Patients receiving anthracyclines and/or trastuzumab in the adjuvant setting should perform serial monitoring of cardiac function at baseline, 3, 6, and 9 months during treatment, and then at 12 and 18 months after the initiation of treatment.
• Monitoring should be repeated during or following treatment as clinically indicated.
Current Means of Cardioprotection

• Cardio-active agents
  – ACE inhibitors
  – Angiotensin receptor blockers
  – Beta-blockers
  – Statins
  – Dexrazoxane* (Anthracyclines)

• Exercise

• Chemotherapy
  – Dose reduction
  – Dosing administration / formulation (e.g., liposomal DOX)
  – Alternative, less toxic agents (e.g., lapatinib)
  – Stop chemotherapy
# Mechanisms of Cardioprotection

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mechanism of Protection</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARBs</td>
<td>Biomechanical effects</td>
<td>BP lowering symptoms (↑ with chemo)</td>
</tr>
<tr>
<td></td>
<td>Antioxidant properties</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Biomechanical effects</td>
<td>BP lowering symptoms (↑ with chemo)</td>
</tr>
<tr>
<td></td>
<td>Antioxidant properties</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>(Carvedilol, Nebivolol)</td>
<td></td>
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<tr>
<td>Statins</td>
<td>Antioxidant properties</td>
<td></td>
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<tr>
<td>Dexrazoxane</td>
<td>Top 2β inhibition</td>
<td>Myelosuppression ? Reduced tumor response rates</td>
</tr>
<tr>
<td></td>
<td>Antioxidant properties</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>Improving CV reserve</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antioxidant effects</td>
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</table>
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*

J Am Coll Cardiol 2006
Primordial Prevention

Protective effects of nebivolol against anthracycline-induced cardiomyopathy: A randomized control study

Kaya et al. Int J Cardiol 2013
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>

Bosch, et al. J Am Coll Cardiol 2013
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

Primordial Prevention

Modulation of Anthracycline-Induced Cardiotoxicity by Aerobic Exercise in Breast Cancer
Current Evidence and Underlying Mechanisms

Jessica M. Scott, PhD; Aarif Khakoo, MD; John R. Mackey, MD; Mark J. Haykowsky, PhD; Pamela S. Douglas, MD; Lee W. Jones, PhD
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

Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection

Kazuaki Negishi\textsuperscript{1†}, Tomoko Negishi\textsuperscript{1†}, Brian A. Haluska\textsuperscript{2}, James L. Hare\textsuperscript{2}, Juan Carlos Plana\textsuperscript{1}, and Thomas H. Marwick\textsuperscript{1,3*}
Primary Prevention

Adapted from Negishi, et al. Eur Heart J Img 2013
Ongoing Trials

• MANTICORE 101-Breast
  – Bisoprolol, perindopril, or placebo on MRI indices of LV remodeling and serum biomarkers in 159 women with HER2+ early breast cancer

• NCT01009918
  – Carvedilol, lisinopril, or placebo on LVEF at 52 weeks in 468 women with HER2+ early breast cancer

• PRADA (NCT01434134)
  – Metoprolol vs. placebo; Candesartan vs. placebo on LVEF by MRI in 120 breast cancer patients receiving anthracyclines or trastuzumab

• NCT00806390
  – Metoprolol vs. placebo on LVEF by MUGA in 188 breast cancer patients receiving anthracyclines or trastuzumab
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 needed to evaluate exercise as intervention
• Future Steps
  • Genetic profiling to characterize risk
  • Personalized cardioprotection?
Thank You