Cardio-Oncology
Toxicities and Management

Duke Debates: Controversies in the Management of Patients with Hematologic Malignancies
April 21, 2017

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Disclosures

• I do not 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

• Financial: Chimerix, Inc. (spouse)
Outline

I. Cardiovascular disease & Cancer Therapy
   a) The basis for Cardio-Oncology
   b) Treatment-related cardiovascular disease (‘cardiotoxicity’)
      i. Traditional and novel anticancer agents
   c) Treatment-independent metabolic adverse effects
   d) Integrated concept of CVD and cancer / cancer therapy

II. What can we do about cardiotoxicity?
   a) Early detection
   b) Prevention & Treatment
THE BASIS FOR CARDIO-ONCOLOGY
I. Survival gains in cancer and CV disease in recent decades

II. Cancer and CV disease pose competing risks:
   i. Cancer survivors remain at risk for CV disease
   ii. CV disease survivors remain at risk for malignancy

III. Cancer therapies can increase CV risk
   I. Toxicities of conventional cancer treatments remain
   II. New ‘targeted’ therapies are being developed rapidly, many of which have recognized or unrecognized cardiovascular toxicities

The Basis for Cardio-Oncology

Why Cardio-Oncology?

Incidence of CV Disease by Cancer Type
Kaiser Permanente (SC)
>36K adult cancer survivors (≥2 years); >73K controls

Armenian, et al. JCO, 2016
The Basis for Cardio-Oncology

Why Cardio-Oncology?

Overall Survival in Cancer among Survivors with and without CV disease
Kaiser Permanente (SC)
>36K adult cancer survivors (≥2 years); >73K controls

Armenian, et al. JCO, 2016
The Basis for Cardio-Oncology
What is Cardio-Oncology?

- Cardiovascular Risk Factors & Disease
- Cancer Therapy: Past & Present
- Cancer Biology & Disease
The Basis for Cardio-Oncology
What is Cardio-Oncology?

Cardiovascular Risk Factors & Disease

Cancer Therapy - Past & Present

- **Acute toxicity** can affect access to life saving drugs
- **Chronic toxicity** can affect survival, morbidity and QOL
Acute Toxicity

50’s yo woman receiving Carfilozimib for multiple myeloma
A few days later ...
The Basis for Cardio-Oncology
What is Cardio-Oncology?

Cardiovascular Risk Factors & Disease

CV and Cancer links

Cancer Therapy Past & Present

Cancer Biology & Disease

• Cancer – CVD relationship not well characterized
• Incident CVD and/or RF’s can limit access to cancer therapies
# Spectrum of Cardio-Oncology

## Cardiotoxicity of cancer treatment

### (Cytotoxic agents, Targeted agents, Radiation, Immunotherapies)

<table>
<thead>
<tr>
<th>Cardiac toxic effects</th>
<th>Vascular toxic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV dysfunction (↓LVEF, ↓GLS)</td>
<td>Accelerated atherosclerosis</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Myocardial ischemia / infarct</td>
<td>VTE events</td>
</tr>
<tr>
<td>Arrhythmia, long QT, SCD</td>
<td>ATE events</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>PAD</td>
</tr>
<tr>
<td>Pericardial constriction</td>
<td>Pulmonary HTN</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>Vasospasm</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>Proteinuria (renovascular)</td>
</tr>
</tbody>
</table>

## Metabolic derangements of cancer/treatment with CV risk

- Glycemic control
- ↓ lean body mass
- ↑ fat mass

## Adverse lifestyle effects of cancer/treatment with CV risk

- Deconditioning / sedentary lifestyle
- Obesity
- Depression / anxiety

## Management of Pre-existing CVD in Cancer

- Anticoagulation / antiplatelet therapy needs
- Arrhythmia (brady- or tachy-), long QT
- Cardiac amyloidosis (e.g., complicating plasma cell dyscrasias)
- Hypertension (essential, renovascular, or secondary)
- Dyslipidemia
- LV dysfunction (↓LVEF, ↓GLS)
- Heart failure
- Ischemic heart disease
- Pulm HTN / Right heart failure / significant TR
- PVD (arterial and/or venous)
CANCER TREATMENT-RELATED CVD (‘CARDIOTOXICITY’)
Spectrum of Cardiotoxicity

## Spectrum of Cardiotoxicity

<table>
<thead>
<tr>
<th>Conventional Therapies</th>
<th>Novel (Targeted) Therapies</th>
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<tbody>
<tr>
<td><strong>Cytotoxic Therapies</strong></td>
<td><strong>Hormonal Therapies</strong></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Endocrine / Androgen Deprivation Therapy (ADT)</td>
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<td>Cardiomyopathy</td>
<td>Metabolic syndrome</td>
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<tr>
<td>Heart Failure</td>
<td>Diabetes</td>
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<tr>
<td>Fluoropyrimidines</td>
<td>CAD</td>
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<td>Myocardial ischemia</td>
<td>VTE</td>
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<tr>
<td>VT / VF / SCD</td>
<td>ATE</td>
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<tr>
<td>MT Inhibitors</td>
<td>↑ CV Events (pre-existing CVD)</td>
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<tr>
<td>Arrhythmias</td>
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<tr>
<td>Alkylating Agents</td>
<td>Trastuzumab</td>
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<td>ATE</td>
<td>Cardiomyopathy</td>
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<tr>
<td>Myocardial ischemia</td>
<td>Heart Failure</td>
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<tr>
<td>Radiation</td>
<td>VEGF Signaling Pathway (VSP) Inhibitors</td>
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<td>Hypertension</td>
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<td>Valvular disease</td>
<td>Cardiomyopathy</td>
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<td>Restrictive CMP</td>
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<td>Radiation</td>
<td>Anti-BCR-ABL TKIs</td>
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<td>Pulmonary HTN</td>
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<td>Radiation</td>
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<td>Hypertension</td>
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<td>Myocardial Ischemia</td>
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<td>Proteosome Inhibitors</td>
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<td>Arrhythmia</td>
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<td>ATE</td>
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<td>Immunomodulators</td>
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<td>ATE, VTE</td>
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<td>HDAC Inhibitors</td>
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<td>Immunotherapies</td>
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<td>BMT</td>
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<td>Dyslipidemia</td>
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<tr>
<td>Cardiomyopathy</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Cytotoxic Therapies and Novel (Targeted) Therapies may include additional side effects such as hypertension, cardiomyopathy, arrhythmias, and metabolic syndrome, depending on the specific treatment.
Anthracycline Cardiotoxicity
Dose related

1979

<400 mg/m²: 0.14%
550 mg/m²: 7%
>700 mg/m²: 18%

2003

<400 mg/m²: 5%
550 mg/m²: 26%

Anthracycline Cardiotoxicity

Time to onset

**Childhood Cancer Experience**

**Congestive heart failure**

- No anthracycline
- <250 mg/m² anthracycline
- ≥250 mg/m² anthracycline

**Cumulative incidence (%)**

- 0
- 2.5
- 5.0
- 7.5
- 10.0

**Time since diagnosis (years)**

- 0
- 10
- 20
- 30

*Mulrooney, et al. BMJ 2009*

**Adult Cancer Experience**

**Proportion Event-free Patients**

- Time since end of chemotherapy (years)
  - 0.80
  - 0.85
  - 0.90
  - 0.95
  - 1.00

**LVEF (%)**

- before CT
- end CT
- 3
- 6
- 9
- 12

*Cardinale, et al. Circulation 2015*
BCR-ABL Kinase Inhibitors

Vascular complications

Dasatinib – Pulmonary Hypertension

9 Patients with PAH
- Median 34 months post-Dasatinib
- 88% women, 67% pleural effusion
- None with complete PAH resolution

Nilotinib – Peripheral arterial disease


<table>
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<tr>
<th>No. of patients (n)</th>
<th>TKI</th>
<th>VAE %</th>
<th>PAOD %</th>
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<td>556</td>
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<td>Ni</td>
<td>nr</td>
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<td></td>
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<td>17.1</td>
<td>11.8</td>
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</tbody>
</table>

Ponatinib – Peripheral arterial disease

- Temporarily withdrawn from market for serious ‘arterial thrombotic events’ in 19% of treated patients
- Resumed sales under narrower indication and black box warning

Radiation Therapy
Childhood Cancer Experience

Mediastinal Radiation Therapy: Effects on Autonomic Function?

Groarke, et al. JACC 2015
Mediastinal Radiation Therapy
Autonomic Dysfunction

Groarke, et al. JACC 2015
Chemoradiation Therapy
Cardiovascular disease in Hodgkins Lymphoma

TREATMENT-INDEPENDENT METABOLIC ADVERSE EFFECTS
Indirect Effects

Cancer treatments

Mediators
- Pro-inflammatory cytokines e.g. IL-6, TNF-α
- Neural e.g. IL-1
- Anabolic e.g. IGF-1
- Catabolic e.g. myostatin

Normal myocardial mass

Comorbid illness
- Advanced age
- Cancer anorexia/
- Food intake
- Physical activity
- Hormonal change e.g.
- Cortisol
- Insulin

Tumour

Ubiquitin proteasome pathway

Autophagy/lysosomal pathway

Apoptosis

Cardiac atrophy

(ΔLVEF)

Skeletal muscle atrophy

↑ Cardiovascular Reserve Capacity

↑ Risk of CVD & Mortality

Multiple hit’ Hypothesis

Cancer Diagnosis

Direct Treatment Effects
- Local Regional Therapy e.g. surgery, radiation
- Systemic Therapy e.g. chemotherapy, endocrine therapy
- Supportive Care e.g. dexamethasone

Indirect Treatment Effects
- Modifiable Risk Factors e.g. ↓ lean body mass, ↑ fat mass, deconditioning, comorbid disease
- Non-modifiable Risk Factors e.g. age, genetics

Adapted from Groarke, et al. Eur Heart J 2013

Adapted from Koelwyn, et al. JACC 2014 and Jones, et al. JACC 2007
CV Effects of Cancer Treatments

• Current anticancer therapies have unique and varying degrees of direct and indirect sequential and progressive CV insults
  – Direct: myocardial toxicity, ischemia, hypertension, arrhythmias
  – Indirect: unfavorable lifestyle changes

• Anthracycline - well-known cardiotoxicity
  – Dose-dependent, irreversible cardiomyocyte necrosis
  – Early- or late-onset LV dysfunction and heart failure

• Targeted agents – emerging recognition of cardiotoxicity
  – Interfere with molecular pathways crucial to CV health
  – Potentially reversible CV effects
CV RISK ASSESSMENT AND CARDIOPROTECTION
**Integrated Concept of CVD & Cancer**

- **Baseline CV health & Risk factors**
- **Cancer Diagnosis**
- **Cytotoxic, Targeted, Radiation Therapy (“CV insult”)**
- **Cardiovascular 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)

Approach to CV Risk Stratification
Hematologist-Oncologist as ‘gatekeeper’

• Assessment of cancer prognosis
  – Age, early-stage vs. advanced disease, disease-site specific
• Assessment of CV disease potential
  – Existing CVD
    • Coronary, valvular, cardiomyopathy, HTN, PAD, arrhythmias, etc.
  – Shared risk factors / co-morbid conditions
    • Smoking, obesity, hyperlipidemia, DM, sedentary, aging
  – Role for CVD risk score(s) (e.g., ASCVD, Framingham, Reynolds, etc.)?
• Assessment of cardiotoxicity potential of proposed treatment(s)
• Cardio-oncology risk assessment
  – Cancer prognosis vs. CVD / cardiotoxicity potential
• Consider acute cardio-oncologic implications
  – Existing CVD or treatment cardiotoxicity potential as barriers to life-saving therapies
• Consider long-term cardio-oncologic implications
  – Development of CVD undermining expected cancer prognosis (survival, QOL, etc.)
Approach to CV protection
The role of the Cardio-Oncologist

CV Risk Threshold Met
Oncologist referral to Cardio-Oncologist

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:
(1) Maintain access to life-saving therapies, and (2) Limit development of CVD

Disadvantages
Duration of treatment uncertain
What can we do about cardiotoxicity?

EARLY DETECTION
Detection
Traditional & 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

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

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

Surveillance

Disease Progression
- Baseline CV health & Risk factors
- Cancer Diagnosis

LV Ejection Fraction

2D Echo

3D Echo
Early detection
3D vs. 2D Echo LVEF


Thavendiranathan, et al. JACC 2012
LVEF Sensitivity for Cardiotoxicity

Myocardial Strain
Speckle-tracking Strain Echocardiography

Strain
Tissue deformation

Strain
% change from resting dimension

L_0
10 cm

L_1
8 cm

-20%

Adapted from Kisslo; Gorcsan, et al. J Am Coll Cardiol 2011
Early detection
Longitudinal Strain vs. 3D Echo LVEF

Post-TCPH
Pre-Trastuzumab
LVEF  54%
GLS  -17%

Trastuzumab x 3M
Pre-Pertuzumab
LVEF  53%
GLS  -11%

Trastuzumab x 5M
Pertuzumab x 2M
LVEF  29%
GLS  -7%
Early detection
Biochemical markers - Troponin

Early detection

Troponin vs. Other Blood-based Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Baseline HR  (95%CI)</th>
<th>p-value†</th>
<th>Visit 2 HR  (95%CI)</th>
<th>p-value†</th>
<th>Interval Change HR  (95%CI)</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>TnI</td>
<td>1.21 (0.92,1.61)</td>
<td>0.177</td>
<td>1.36 (1.07,1.73)</td>
<td>0.012</td>
<td>1.38 (1.05,1.81)</td>
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<td>NT-proBNP</td>
<td>0.78 (0.48,1.25)</td>
<td>NS</td>
<td>0.89 (0.59,1.35)</td>
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<td>CRP</td>
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<td>1.07 (0.72,1.60)</td>
<td>NS</td>
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<td>GDP-15</td>
<td>0.90 (0.59,1.37)</td>
<td>NS</td>
<td>1.26 (0.89,1.78)</td>
<td>0.189</td>
<td>1.33 (0.93,1.92)</td>
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<td>MPO</td>
<td>0.66 (0.44,1.00)</td>
<td>0.052</td>
<td>1.23 (0.93,1.62)</td>
<td>0.149</td>
<td>1.34 (1.00,1.80)</td>
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<td>PIGF</td>
<td>0.88 (0.55,1.40)</td>
<td>NS</td>
<td>1.17 (0.82,1.65)</td>
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<td>1.16 (0.77,1.73)</td>
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<td>sFlt-1</td>
<td>1.05 (0.70,1.56)</td>
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<td>0.76 (0.54,1.06)</td>
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<td>0.75 (0.51,1.10)</td>
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<td>Gel-3</td>
<td>0.70 (0.44,1.11)</td>
<td>0.128</td>
<td>0.94 (0.62,1.41)</td>
<td>NS</td>
<td>1.33 (0.86,2.05)</td>
<td>0.195</td>
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Early detection

Echo Strain vs. Troponin

- 81 breast cancer patients; HER2+
- Mean LVEF 64±5% → 59±6% (P < 0.0001) over 15 months
- Cardiotoxicity (n = 26) defined by CREC criteria and heart failure (n = 5)
- μs Troponin I and Echo longitudinal strain at anthracycline completion
  - Predicted subsequent development of cardiotoxicity
- *Longitudinal strain only independent predictor of cardiotoxicity and LVEF <50%
Prognostic Value of Echo
Traditional & Novel Parameters

Cardiac Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chi-square</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Clinical</td>
<td>60</td>
<td>.014</td>
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<tr>
<td>Clinical+LVEF</td>
<td>110</td>
<td>&lt;.001</td>
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<tr>
<td>Clinical+LVEF+GLS</td>
<td>150</td>
<td>&lt;.001</td>
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Cardiotoxicity

<table>
<thead>
<tr>
<th>Parameter Combinations</th>
<th>Chi-square</th>
<th>P-value</th>
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<tr>
<td>Clinical</td>
<td>8</td>
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<tr>
<td>Clinical + EF</td>
<td>10</td>
<td>.03</td>
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<tr>
<td>Clinical + EF + e'</td>
<td>12</td>
<td>.06</td>
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<td>Clinical + EF + s'</td>
<td>11</td>
<td>.05</td>
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<tr>
<td>Clinical + EF + GLSR-S</td>
<td>14</td>
<td>.0008</td>
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<tr>
<td>Clinical + EF + GLSR-E</td>
<td>16</td>
<td>.0008</td>
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</tbody>
</table>

Negishi, et al. JASE 2013
## Modalities of Cardiotoxicity Detection

<table>
<thead>
<tr>
<th></th>
<th>Echocardiography</th>
<th>RNA (MUGA)</th>
<th>cMR</th>
<th>Blood Biomarkers</th>
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<td></td>
<td>2D</td>
<td>3D</td>
<td>Strain</td>
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<tr>
<td><strong>Target(s)</strong></td>
<td>LVEF; LV Vol</td>
<td>LVEF; LV Vol</td>
<td>Myocardial deformation</td>
<td>LVEF; LV Vol</td>
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<tr>
<td><strong>Availability</strong></td>
<td>+++</td>
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<tr>
<td><strong>Cost</strong></td>
<td>Low</td>
<td>Medium</td>
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</tr>
<tr>
<td><strong>Reproducibility</strong></td>
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<td><strong>Cardiac structure</strong></td>
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<tr>
<td><strong>Temporal resolution</strong></td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
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<tr>
<td><strong>Spatial resolution</strong></td>
<td>++</td>
<td>+</td>
<td>+++</td>
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<td><strong>Myocardial function</strong></td>
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<tr>
<td><strong>Systolic</strong></td>
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<td><strong>Diastolic</strong></td>
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<td><strong>Tissue characterization</strong></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Potential to detect subclinical cardiac toxicity</strong></td>
<td>Low</td>
<td>Low</td>
<td>Moderate-High</td>
<td>Low</td>
</tr>
</tbody>
</table>

Current State of Detection in Cardiotoxicity

• Current standard detection modalities in cardio-oncology (i.e., resting LVEF) are insensitive for cardiotoxicity and may not be prognostic
• Emerging imaging modalities that assess myocardial deformation, functional capacity testing, and blood biomarkers have potential to improve early detection
• However, evidence with these modalities remains based on small, single center studies
• Future investigation with large, prospective studies is required to validate their diagnostic and prognostic utility, determine optimal timing of assessments, and standardize cut-off points
What can we do about cardiotoxicity?

PREVENTION & TREATMENT
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

- Echocardiography
- Nuclear cardiology

Diagnosis

- Cytotoxic, Targeted, Radiation Therapy ("CV insult")

Guide treatment

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

Disease Progression

- Baseline CV health & Risk factors
- Cancer Diagnosis
- Heart failure (ACC/AHA Stage C & D)

Prevention and Treatment

- ACE inhibitors / Angiotensin Receptor Blockers
- Beta blockers
- Aldosterone Antagonists
- Statins
- Dexrazoxane
- Exercise

For effective cardioprotection, timing is the key...
Current Means of Cardioprotection

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

- Exercise

- Chemotherapy
  - Dose reduction
  - Dosing administration / formulation (e.g., liposomal DOX)
  - Alternative, less toxic agents (e.g., lapatinib, pertuzumab)
  - Stop chemotherapy
Primordial Prevention

Beta Blockers

Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy

Nihat Kahy, MD,* Emrullah Basar, MD,* Ibrahim Ozdogru, MD,* Oleten Er, MD;† Yakup Cetinkaya, MD;* Ali Dogan, MD;* Tugrul Inanc, MD; Abdurrahman Oguzhan, MD;* Nanik Kemal Eryol, MD;* Ramazan Topacak, MD;* Ali Ergin, MD

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

Kaya, et al. Int J Cardiol 2013

\[ p = 0.01 \]

\[ p = 0.01 \]

\[ p = 0.12 \]

\[ p = 0.01 \]
Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

The OVERCOME Trial (prevention of left Ventricular Dysfunction)

<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>0.029</td>
</tr>
</tbody>
</table>
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,† Andrea Seicean, MPH,‡ Juan Carlos Plana, MD,‡ G. Thomas Budd, MD,§ Thomas H. Marwick, MD, PhD, MPH‡

Statins

Controls

p=0.03
### Primordial Prevention

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Dextrozoxane Vs Control</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lopez 1998</td>
<td>4</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Marty 2006</td>
<td>10</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Speyer 1992</td>
<td>6</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Swahn-1 1997</td>
<td>25</td>
<td>168</td>
<td></td>
</tr>
<tr>
<td>Swahn-2 1997</td>
<td>11</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Venturini 1996</td>
<td>6</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Wexler 1996</td>
<td>4</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>569</td>
<td>593</td>
<td>0.35 [0.27, 0.45]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>66</td>
<td>196</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi² = 6.43, df = 6 (P = 0.38); I² = 7%</td>
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<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 8.15 (P &lt; 0.00001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.1.2 Beta Blocker Vs Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosch -1 2013</td>
<td>3</td>
<td>46</td>
<td></td>
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<tr>
<td>Kalay 2006</td>
<td>1</td>
<td>25</td>
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<tr>
<td>Seicean-1 2012</td>
<td>5</td>
<td>106</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>176</td>
<td>282</td>
<td>0.31 [0.16, 0.65]</td>
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<tr>
<td><strong>Total events</strong></td>
<td>9</td>
<td>43</td>
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<tr>
<td><strong>Heterogeneity:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi² = 0.36, df = 2 (P = 0.84); I² = 0%</td>
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<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 3.30 (P &lt; 0.0010)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.1.3 Statin Vs Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acar 2011</td>
<td>1</td>
<td>20</td>
<td></td>
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<tr>
<td>Seicean-2 2012</td>
<td>4</td>
<td>67</td>
<td></td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>87</td>
<td>154</td>
<td>0.31 [0.13, 0.77]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>5</td>
<td>28</td>
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</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi² = 0.22, df = 1 (P = 0.64); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 2.52 (P = 0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.1.4 Angiotensin antagonist vs control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosch -2 2013</td>
<td>3</td>
<td>45</td>
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<tr>
<td>Cardinali 2006</td>
<td>0</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Nakamae 2005</td>
<td>0</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>121</td>
<td>123</td>
<td>0.11 [0.04, 0.29]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>3</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi² = 4.20, df = 2 (P = 0.12); I² = 52%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 4.34 (P &lt; 0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>953</td>
<td>1152</td>
<td>0.31 [0.25, 0.39]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>83</td>
<td>304</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi² = 12.16, df = 14 (P = 0.59); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 10.24 (P &lt; 0.00001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for subgroup differences:</strong></td>
<td>Chi² = 5.03, df = 3 (P = 0.17), I² = 40.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary Prevention
Troponin + ACE Inhibitors

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

Primary Prevention
Strain + Beta Blockers

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

Kazuaki Negishi, Tomoko Negishi, Brian A. Haluska, James L. Hare, Juan Carlos Plana, and Thomas H. Marwick

Baseline 
Follow-up 1 
Follow-up 2

<11% (n=107) 

ΔGLS <11% (n=159)

ΔGLS ≥11% (n=52)

Beta-blocker (-) (n=28)

Beta-blocker (+) (n=24)

Eur Heart J Img 2013
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 Guidelines in Cardio-Oncology

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines
The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

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

Plana, et al. JASE, 2014
Prevention / Treatment

• ACE inhibitors or Beta blockers are recommended after detection of cardiotoxicity by LVEF decline
  – Promising data for ACEI’s, B-BI’s (emerging for statins)
  – However, large randomized / prospective trials needed
    • Optimal timing of intervention? What detection method is best?
    • Primordial prevention? Revisit use of Dexrazoxane?
    • Duration of therapy?
    • Intra-class differences among beta blockers, ACE inhibitors, etc.?

• Studies needed to evaluate exercise as intervention

• Future Steps
  – Genetic profiling to characterize risk
    • Personalized cardioprotection?
The Goal of Cardio-Oncology

Cardiovascular Risk Factors & Disease

Cancer Therapy
Past & Present

Cancer Biology & Disease

Cardio-Oncology

CV OUTCOMES

CANCER OUTCOMES
Thank You