Detection and Surveillance of Cancer Therapy-Induced Cardiotoxicity in Women

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@datsunian  #bruinhearts
Disclosures

- Assistant Editor, Editorial Board, **JACC: Cardio-Oncology**
  - No financial conflicts of interest

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- Consulting Fees
  - Pfizer, Edwards Lifesciences (nonrelevant)
Learning Objectives

1. Emphasize the growing importance of recognizing and treating cardiovascular disease in the growing cancer population

2. Review clinical trials evaluating cardioprotective strategies in cancer treatment associated cardiotoxicities in women

3. Highlight key points from recent consensus statements of cardiotoxicity surveillance for cancer treatment induced cardiomyopathy

4. Review clinical presentations of cardiotoxicities unique to cancer treatments

5. Discuss potential links of cardiotoxicity to health disparities in vulnerable/underresourced populations, especially in female populations

Scan QR code with smartphone camera to access literature
Why Talk About Cancer?
Cardiovascular and Cancer Deaths by Sex in US 2022

**Graph 1:**
- CVD: NH White Males 28.4%, NH White Females 27.6%
- Cancer: NH White Males 19.3%, NH White Females 17.9%
- COVID-19: NH White Males 8.6%, NH White Females 8.2%
- Accidents: NH White Males 7.0%, NH White Females 4.2%
- CLRD: NH White Males 4.6%, NH White Females 5.7%
- Alzheimer Disease: NH White Males 2.6%, NH White Females 6.2%

**Graph 2:**
- CVD: Hispanic Males 21.1%, Hispanic Females 23.4%
- COVID-19: Hispanic Males 23.3%, Hispanic Females 18.8%
- Cancer: Hispanic Males 16.3%, Hispanic Females 12.9%
- Accidents: Hispanic Males 4.3%, Hispanic Females 4.4%
- Diabetes: Hispanic Males 4.1%, Hispanic Females 4.4%
- Alzheimer Disease: Hispanic Males 1.7%, Hispanic Females 5.2%

*Source: Circulation. 2023;147:e93–e621.*
Trends in Cancer Death Rates Overall by Site and Gender in US

Cancer statistics, 2023

[Graph showing trends in cancer death rates by site and gender in the US over different years.]
Current State of Cancer Survivors

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate</strong></td>
<td>3,650,030</td>
<td>Breast</td>
</tr>
<tr>
<td><strong>Colon &amp; rectum</strong></td>
<td>776,120</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td><strong>Melanoma of the skin</strong></td>
<td>684,470</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td><strong>Urinary bladder</strong></td>
<td>624,480</td>
<td>Thyroid</td>
</tr>
<tr>
<td><strong>Non-Hodgkin lymphoma</strong></td>
<td>400,070</td>
<td>Melanoma of the skin</td>
</tr>
<tr>
<td><strong>Kidney &amp; renal pelvis</strong></td>
<td>342,060</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td><strong>Testis</strong></td>
<td>287,780</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td><strong>Lung &amp; bronchus</strong></td>
<td>258,200</td>
<td>Cervix</td>
</tr>
<tr>
<td><strong>Leukemia</strong></td>
<td>256,790</td>
<td>Ovary</td>
</tr>
<tr>
<td><strong>Oral cavity &amp; pharynx</strong></td>
<td>249,330</td>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td><strong>All sites</strong></td>
<td>8,138,790</td>
<td>All sites</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate</strong></td>
<td>5,017,810</td>
<td>Breast</td>
</tr>
<tr>
<td><strong>Colon &amp; rectum</strong></td>
<td>994,210</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td><strong>Melanoma of the skin</strong></td>
<td>936,980</td>
<td>Thyroid</td>
</tr>
<tr>
<td><strong>Urinary bladder</strong></td>
<td>832,910</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td><strong>Non-Hodgkin lymphoma</strong></td>
<td>535,970</td>
<td>Melanoma of the skin</td>
</tr>
<tr>
<td><strong>Kidney &amp; renal pelvis</strong></td>
<td>476,910</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td><strong>Testis</strong></td>
<td>361,690</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td><strong>Leukemia</strong></td>
<td>352,900</td>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td><strong>Lung &amp; bronchus</strong></td>
<td>325,680</td>
<td>Ovary</td>
</tr>
<tr>
<td><strong>Oral cavity &amp; pharynx</strong></td>
<td>315,730</td>
<td>Uterine cervix</td>
</tr>
<tr>
<td><strong>All sites</strong></td>
<td>10,995,610</td>
<td>All sites</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Estimated Number of US Cancer Survivors by Site. Estimates do not include in situ carcinoma of any site except urinary bladder and do not include basal cell or squamous cell skin cancers.
Cardiovascular Disease Risk Among Cancer Survivors

The Atherosclerosis Risk In Communities (ARIC) Study

Robertetta Florido, MD, MHS,① ② Natalie R. Daya, MPH,① Chiadi E. Ndumele, MD, PhD, MHS,① ② Silvia Koton, PhD, MOC-H, RN,②⑧ Stuart D. Russell, MD,① Anna Prizment, PhD,① Roger S. Blumenthal, MD,① ⑧ Kunihiro Matsushita, MD, PhD,①②⑧ Yejin Mok, PhD, MPH,① Ashley S. Felix, PhD, MPH,① Josep Coresh, MD, PhD,① Carmen F. Iothu, PhD,①② Elizabeth A. Platz, ScD, MPH,①②⑧ Elizabeth Selvin, PhD, MPH,①②⑧

Central Illustration: Cardiovascular Disease Risk in Cancer Survivors and Proposed Pathways Linking Cancer and Cardiovascular Disease

### Proposed Pathways Related to Cancer

- Toxicities of cancer therapies
- Physiologic effects of cancer (inflammation, oxidative stress, etc.)
- Common biological predisposition (genetics, clonal hematopoiesis, etc.)

### Traditional Risk Factors

Traditional risk factors such as lifestyle practices, smoking, diabetes, and obesity do not account for all the excess risk of CVD in cancer survivors.

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**Figure 1:** Association of Cancer Survivors With CVD by Cancer Type

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>N</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Cancer</td>
<td>12,421</td>
<td>1.37 (1.26-1.50)</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>6,656</td>
<td>1.32 (1.08-1.60)</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>5,538</td>
<td>1.10 (0.92-1.32)</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>12,421</td>
<td>2.37 (1.84-3.06)</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>12,421</td>
<td>1.46 (1.15-1.85)</td>
</tr>
<tr>
<td>Hematopoietic and Lymphatic Cancer</td>
<td>12,421</td>
<td>2.70 (2.04-3.59)</td>
</tr>
</tbody>
</table>

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Cancer-related pathways underlying the associations of cancer with CVD include, but are not limited to, common biological predisposition, inflammation, oxidative stress, a prothrombotic state promoted by the cancer itself, and cardiotoxic effects of various cancer therapies. Non-cancer-related pathways include lifestyle factors such as diet and physical activity, and shared risk factors between cancer and CVD, such as smoking, obesity, and diabetes. CVD = cardiovascular disease.
Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study

Jennifer L. Patnaik1, Tim Byers2, Carolyn DiGuseppi3, Dana Dabelea1 and Thomas D Denberg2

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>3,861,520</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>807,860</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>768,650</td>
</tr>
<tr>
<td>Thyroid</td>
<td>705,050</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>672,140</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>357,650</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>313,140</td>
</tr>
<tr>
<td>Cervix</td>
<td>283,120</td>
</tr>
<tr>
<td>Ovary</td>
<td>249,230</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>227,510</td>
</tr>
<tr>
<td>All sites</td>
<td>8,781,580</td>
</tr>
</tbody>
</table>

Figure 2 Proportional distribution of cumulative leading causes of death by time since breast cancer diagnosis. CVD: cardiovascular disease.

http://breast-cancer-research.com/content/13/3/R64
Cardiovascular Disease and Breast Cancer: Where These Entities Intersect
A Scientific Statement From the American Heart Association

Figure 2. Risk factors for cardiovascular disease (CVD) and breast cancer. CVD and breast cancer have shared and separate risk factors.¹⁹,²⁹–³¹
Biological Underpinnings of Cardio-Oncology

Adapted From Dr. Michel Khouri, MD, Duke University

- Treatment-related “Cardiotoxicity”
- Acute toxicity can affect access to life saving drugs
- Chronic toxicity can affect survival, morbidity & QOL
### What is Defined As Cardiotoxicity?

<table>
<thead>
<tr>
<th>CTRCD</th>
<th>Very severe</th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic CTRCD (HF)</td>
<td>HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation</td>
<td>HF hospitalization</td>
<td>Need for outpatient intensification of diuretic and HF therapy</td>
<td>Mild HF symptoms, no intensification of therapy required</td>
</tr>
<tr>
<td>Asymptomatic CTRCD</td>
<td></td>
<td>New LVEF reduction to &lt;40%</td>
<td>New LVEF reduction by ≥10 percentage points to an LVEF of 40–49% OR New LVEF reduction by &lt;10 percentage points to an LVEF of 40–49% AND either new relative decline in GLS by &gt;15% from baseline OR new rise in cardiac biomarkers</td>
<td>LVEF ≥ 50% AND new relative decline in GLS by &gt;15% from baseline AND/OR new rise in cardiac biomarkers</td>
</tr>
</tbody>
</table>

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[Table 3: Cancer therapy-related cardiovascular toxicity definitions](#)
### Table 4

Heart Failure Association–International Cardio-Oncology Society baseline cardiovascular toxicity risk stratification

<table>
<thead>
<tr>
<th>Baseline CV toxicity risk factors</th>
<th>Anthracycline chemotherapy</th>
<th>HER2-targeted therapies</th>
<th>VEGF inhibitors</th>
<th>BCR-ABL inhibitors</th>
<th>Multiple myeloma therapies</th>
<th>RAF and MEK inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF/cardiomyopathy/CTRCD</td>
<td>VH</td>
<td>VH</td>
<td>VH</td>
<td>H</td>
<td>VH</td>
<td>VH</td>
</tr>
<tr>
<td>Severe VHD</td>
<td>H</td>
<td>H</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>H</td>
</tr>
<tr>
<td>MI or PCI or CABG</td>
<td>H</td>
<td>H</td>
<td>VH</td>
<td>–</td>
<td>–</td>
<td>H</td>
</tr>
<tr>
<td>Stable angina</td>
<td>H</td>
<td>H</td>
<td>VH</td>
<td>–</td>
<td>–</td>
<td>H</td>
</tr>
<tr>
<td>Arterial vascular disease</td>
<td>–</td>
<td>–</td>
<td>VH</td>
<td>VH</td>
<td>VH</td>
<td>–</td>
</tr>
<tr>
<td>Abnormal ankle-brachial pressure index</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PH</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>H</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Arterial thrombosis with TKI</td>
<td>–</td>
<td>–</td>
<td>VH</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
Care Pathways

Baseline CV toxicity risk assessment checklist

- Age, sex, genetics
- Previous CVD
- Medical CVRF
- Previous cardiotoxic therapies
- ECG, TTE, and cardiac biomarkers abnormalities

CTR-CVT risk factors

Clinical assessment
- Cancer treatment history
- CV history
- CVRF
- Physical examination
- Vital signs measurement

Complementary tests
- BNP or NT-proBNP
- cTn
- ECG
- Fasting plasma glucose / HbA1c
- Kidney function / eGFR
- Lipid profile
- TTE

Cardio-Oncology Care Pathways

- New cancer diagnosis
- During cancer treatment
- First year after cancer treatment
- Long term follow-up

Baseline CV toxicity risk assessment

Low risk patients

Moderate risk patients

High and very high risk patients

Cardiology referral if new CV signs/symptoms or CTR-CVT develop

Class 1

Class 1a

Class 1b
Incidence of Cancer Treatment Associated Cardiomyopathy in Modern Trials

Heart Failure

Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

Long-Term Risk of Heart Failure in Breast Cancer Patients After Adjuvant Chemotherapy With or Without Trastuzumab

HR 8.7 (95% CI 4.6-16.5) for early HF
HR 1.9 (95% CI: 1.2-3.3) for late HF

Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity
The CECCY Trial
13.5-14.5%
Cardioprotective Strategies: What Works and What Doesn’t
Trastuzumab (Anti-HER2)
### Anthracycline chemotherapy surveillance protocol

**Low risk**
- Baseline
- ECG
- TTE
- cTn / NtProBNP

**Moderate risk**
- ECG
- TTE
- cTn / NtProBNP

**High and very high risk**
- ECG
- TTE
- cTn / NtProBNP

---

### Recommendations

<table>
<thead>
<tr>
<th>TTE</th>
<th>Class</th>
<th>Level</th>
<th>Cardiac serum biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline measurement of NP and cTn is recommended in high- and very high-risk patients prior to anthracycline chemotherapy.</td>
</tr>
</tbody>
</table>

**Baseline echocardiography** is recommended in all patients with cancer before anthracycline chemotherapy.

In all adults receiving anthracycline chemotherapy, an echocardiogram is recommended within 12 months after completing treatment.

In high- and very high-risk patients, echocardiography is recommended every two cycles and within 3 months after completing treatment.

In moderate-risk patients, additional echocardiography should be considered after a cumulative dose of ≥ 250 mg/m² of doxorubicin or equivalent.

In low-risk patients, additional echocardiography may be considered after a cumulative dose of ≥ 250 mg/m² of doxorubicin or equivalent.
Anthracycline Induced Cardiomyopathy

Pre-Chemotherapy

History of Idarubicin exposure for acute leukemia

Beta Blockers?
ACE-I?
ARB?
Dexrazoxane?

Post-Chemotherapy After 2-3 Months
**Low Risk Patient?**

### Trial Design
Patients with HER2-negative breast cancer undergoing anthracycline-based chemotherapy were randomized to carvedilol (n = 96) vs. placebo (n = 96). Follow-up was 24 weeks.

### Results
- Prevention of a ≥10% reduction in left ventricular ejection fraction (LVEF) at 6 months: 14.5% of the carvedilol group vs. 13.5% of the placebo group (p = 1.0).
- Percentage of patients with troponin I ≥0.04: 26.0% vs. 41.6% (p = 0.003).

### Conclusions
- Among patients with invasive breast cancer undergoing anthracycline-based chemotherapy, carvedilol versus placebo was not effective at preventing a reduction in LVEF.
- Carvedilol was associated with a lower frequency of detectable troponin I values.

Avila MS, et al. J Am Coll Cardiol 2018;Mar 11 [Epub]
- Meta-analysis of 17 RCTs of 1,984 patients undergoing chemotherapy
- Neurohormonal tx (BB, ACE-I/ARB) vs placebo
- Pooled analysis overall 3.96% (95% CI: 2.90-5.02) increase in LVEF
- Significant heterogeneity
- Nonsignificant trend towards lower adverse clinical events
Statins?

No benefit in breast cancer

Less decrease in LVEF in lymphoma

With atorvastatin 40 mg daily
Dexrazoxane

- Iron-chelating agent that reduces formation of iron-anthracycline complexes
- Limits generation of reactive oxygen species and thus toxicity of anthracyclines
- Interferes with topoisomerase 2β antagonizing doxorubicin induced DNA damage
- FDA approved in 2011 for advanced/metastatic breast cancer who have received at least 300 mg/m2 of doxorubicin
- Concern for secondary malignancies of AML and MDS in children

Clinical Heart Failure/Cardiac Events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Dexrazoxane Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopez 1998</td>
<td>0</td>
<td>43</td>
<td>2</td>
<td>0.63 [0.41, 1.00]</td>
</tr>
<tr>
<td>Marty 2006</td>
<td>1</td>
<td>85</td>
<td>7</td>
<td>1.35 [0.95, 1.90]</td>
</tr>
<tr>
<td>Speyer 1992</td>
<td>2</td>
<td>76</td>
<td>4</td>
<td>2.84 [1.90, 4.25]</td>
</tr>
<tr>
<td>Sun 2015</td>
<td>0</td>
<td>40</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Swain 1997 (a)</td>
<td>0</td>
<td>168</td>
<td>13</td>
<td>0.72 [0.50, 1.03]</td>
</tr>
<tr>
<td>Swain 1997 (b)</td>
<td>2</td>
<td>81</td>
<td>7</td>
<td>2.40 [1.50, 3.76]</td>
</tr>
<tr>
<td>Venturin 1996</td>
<td>2</td>
<td>52</td>
<td>100</td>
<td>1.00 [0.49, 2.00]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>575</td>
<td>605</td>
<td>100%</td>
<td>0.19 [0.09, 0.40]</td>
</tr>
</tbody>
</table>

Total events: 7 vs 58
Heterogeneity: Tau² = 0.00; Chi² = 4.74, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 4.96 (P < 0.0001)

<table>
<thead>
<tr>
<th>1.1.2 Cardiac events</th>
<th>Dexrazoxane Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopez 1998</td>
<td>0</td>
<td>44</td>
<td>13</td>
<td>1.20 [0.67, 2.16]</td>
</tr>
<tr>
<td>Marty 2006</td>
<td>10</td>
<td>85</td>
<td>79</td>
<td>1.65 [1.06, 2.55]</td>
</tr>
<tr>
<td>Speyer 1992</td>
<td>5</td>
<td>76</td>
<td>74</td>
<td>1.20 [0.67, 2.16]</td>
</tr>
<tr>
<td>Swain 1997 (a)</td>
<td>25</td>
<td>168</td>
<td>57</td>
<td>3.01 [1.31, 6.82]</td>
</tr>
<tr>
<td>Swain 1997 (b)</td>
<td>11</td>
<td>81</td>
<td>32</td>
<td>1.04 [0.42, 2.56]</td>
</tr>
<tr>
<td>Tahover 2017</td>
<td>2</td>
<td>104</td>
<td>71</td>
<td>2.02 [1.50, 2.71]</td>
</tr>
<tr>
<td>Venturin 1996</td>
<td>6</td>
<td>82</td>
<td>78</td>
<td>1.05 [0.54, 2.02]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>683</td>
<td>1414</td>
<td>100%</td>
<td>0.36 [0.27, 0.49]</td>
</tr>
</tbody>
</table>

Total events: 64 vs 219
Heterogeneity: Tau² = 0.03; Chi² = 8.55, df = 7 (P = 0.29); I² = 18%
Test for overall effect: Z = 2.49 (P < 0.0001)
Primary and secondary cancer-therapy related CV toxicity prevention strategies

**Primary vs secondary prevention**

- **Baseline CV risk assessment**
  - **1st prevention**
  - **2nd prevention**

**Management of CVD and CVRF according to ESC Guidelines**

- In patients at high and very high risk of CTRCD
  - Minimize the use of cardiotoxic drugs
    - ACE-I/ARB and beta-blockers
    - Dexrazoxane/liposomal anthracyclines (patients treated with anthracyclines)
  - Statins

**Class I**

- 1st cancer requiring cardiotoxic cancer therapy
- 2nd cancer requiring cardiotoxic cancer therapy
- CVD
- CTR-CYT

**Class IIa**

- ECV

ESC European Society of Cardiology
What If Cardiotoxicity Occurs?

Permissive Cardiotoxicity
The Clinical Crucible of Cardio-Oncology

A proactive approach to continuing important cancer therapies while mitigating associated cardiotoxicity given the oncologic benefits.
SCHOLAR Trial

• Safety of Continuing Chemotherapy in Overt Left Ventricular Dysfunction Using Antibodies to Human Epidermal Growth Factor Receptor-2 [SCHOLAR]
  
  • Phase I, prospective, single-arm trial
  • Continuation of trastuzumab in patients with:
    • LVEF between 40% and the lower limit of normal
    • Or if LVEF fell >15% from baseline
  • Titrated on cardioprotective medications (ACEi/ARB and/or B-blocker)
  • Primary outcome: cardiac dose-limiting toxicity, defined as cardiovascular death, LVEF<40% and heart failure symptoms, or LVEF<35%
  • 20 patients with Stage I-III breast cancer
Outcomes

- 18/20 patients (90%) completed trastuzumab cancer treatments
- 2/20 patients (10%) developed cardiac dose-limiting cardiotoxicity
  - EF for both patients → 56% and 47% respectively off trastuzumab
  - No patient deaths
- ACE inhibitor – Ramipril
- ARB – Candesartan
- B-blocker – Carvedilol/bisoprolol

The Immunotherapy Revolution…
And a New Disease Process
Releasing the Brakes on Cancer Immunotherapy
Antoni Ribas, M.D., Ph.D.

Figure 1. T-Cell Activation in the Lymph Node.

Figure 2. T-Cell Activation in the Tumor Milieu.

DOI: 10.1056/NEJMp1510079
#bruinhearts
Figure 1. Percentage of US Patients With Cancer Who May Benefit From and Respond to Checkpoint Inhibitor Immunology Drugs (2011-2018)
ICI Associated Myocarditis

- Incidence ~1%
- Dramatic increase in reporting incidence over time, likely due to increased use of ICI and increased reporting
- Risk Factors
  - Combination ICI therapy: 4.74-fold risk compared to monotherapy
    - Increased risk of severe myocarditis
    - Increased rates of co-occurring myasthenia gravis and myositis
    - Increased mortality
  - Compared to other forms of myocarditis
    - Female Sex (?)
    - Age > 75yo (compared to other forms of myocarditis)

Mahmood et al. JACC 2018
Zamami et al. JAMA Onc 2019
Hu et al. Cardiovascular Research 2019
ICI Associated Myocarditis - Presentation

• Clinical Symptoms
  • Acute heart failure
  • Chest pain
  • SOB
  • Pulmonary edema
  • Cardiogenic Shock
  • Arrhythmia
    • Heart block
    • Atrial arrhythmias
    • Ventricular arrhythmias

• Timing of Onset:
  • 1-2 months from first treatment
  • 76% occurred within the first 6 weeks.
  • In another case series, 81% occurred within 3 months of initiating therapy

Mahmood et al. JACC 2018  Moslehi et al. Lancet 2018
Prognosis

• **Mahmood et al:**
  - 46% of cases experienced a MACE
    - Cardiovascular death, cardiogenic shock, cardiac arrest, or CHB
  - Low EF was not associated with risk of MACE
  - Troponin T >1.5 ng/dl had 95% specificity for development of MACE
  - LVEF normal in ~50% of pts

• **Moslehi et al:**
  - 101 patients
  - Mortality of 46%

• In survivors, complete recovery of EF was seen in 50%
ICI Associated Myocarditis - Diagnosis

- Endomyocardial biopsy:
  - CD4+ and CD8+ T cells
  - CD68+ macrophages
  - Involving the myocardium, conduction system and skeletal muscle
ICI Associated Myocarditis – Associated Toxicities

• Frequently patients have other immune side effects with multiorgan involvement

• Increased association with:
  • Myositis 25%
  • Myasthenia Gravis 10-11%
  • Evaluate for multiorgan involvement

---

**TABLE 2 Baseline Cancer Demographics**

<table>
<thead>
<tr>
<th></th>
<th>Myocarditis (n = 35)</th>
<th>Control (n = 105)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other immune side effects during treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No other immune side effects</td>
<td>19 (54.0)</td>
<td>61 (58.0)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypophysitis/pituitary/adrenal</td>
<td>3 (8.6)</td>
<td>6 (5.7)</td>
<td>0.69</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (8.6)</td>
<td>11 (10.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>7 (20.0)</td>
<td>5 (4.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Colitis</td>
<td>4 (11.0)</td>
<td>15 (14.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>4 (11.0)</td>
<td>3 (2.9)</td>
<td>0.065</td>
</tr>
<tr>
<td>Neurological</td>
<td>4 (11.0)</td>
<td>3 (2.9)</td>
<td>0.065</td>
</tr>
<tr>
<td>Gastritis</td>
<td>0 (0.0)</td>
<td>4 (3.8)</td>
<td>0.57</td>
</tr>
</tbody>
</table>
Check your Biomarkers!

Original Research

Biomarker Trends, Incidence, and Outcomes of Immune Checkpoint Inhibitor-Induced Myocarditis

Alesa Vakhshura, PhD, RN, b,c YeeAnn Chen, Pasa, D, a,Adrian Procureur, MD, a Allison Gradone, MD, a, Tariq U. Aziz, MD, b Daniel Perry, MD, c Hassan Shafi, MD, c Elizabeth Anderson, MPH, d Yomimari Arai, BS, d Penelope Blakely, BS, d Namitha Nelapudi, b, Mohamed Fardous, a Marie C. Bratage, MD, e Sarah K. Adie, Pas, d, RCCP, d Kristen T. Pegar, Pas, d, d Monika Leja, MD, d Sarah Yente, MD, d Bryan Schaeffer, MD, d Leslie A. Ferhi, MD, d Christopher D. Lee, MD, d Joe-Elle Saleri, MD, PhD, d Salim S. Hayek, MD

#bruinhearts
Case Study: ICI Myocarditis

- 60 year old female with BRAF+ colorectal CA
  - post XELOX and nivolumab (3 cycles)
- Presenting with cardiogenic shock from ICI myocarditis
  - Impella
  - VA ECMO support
  - ATG, steroids

- Services involved
  - Cardio-Oncology
  - Oncology
  - Cardiomyopathy
  - Interventional Cardiology
  - Cardiothoracic Surgery
  - Critical Care Anesthesia

12 lead ECG demonstrating ventricular/fascicular tachycardia with diffuse ST elevations

Transthoracic echocardiography showing LVEF<20% with Impella device for mechanical circulatory support

Endomyocardial biopsy H&E 20X
Diffuse lymphocytic infiltration of myocardium c/w ICI myocarditis
ICI Myocarditis (Suggested) Treatment Strategies

Management of patients with a definitive diagnosis of ICI-related myocarditis

Severity (fulminant vs. non-fulminant)

Discontinue ICI; hospital admission; ECG monitoring (Class I)

Methylprednisolone 500–1000 mg iv bolus once daily (minimum 3 days) (Class I)

Recovering

Steroid refractory

Haemodynamically unstable fulminant myocarditis

Switching to oral prednisolone (1 mg/kg/day) (Class IIa)

Second-line immunosuppression (Class IIa)

Admission to ICU (level 3) (Class I)

AND

Optimal CV treatment including MCS (Class I)

AND

Second-line immunosuppression (Class I)

Complete recovery

Antithymocyte globulin
Abatacept+/-
Ruxolitinib
Mycophenolate
Avoid infliximab

#bruinhearts
Racial and Ethnic Disparities in Cardio-Oncology
A Call to Action

Muhammad Fazal, MD, MS,a,b Jessica Malisa, BA,b June-Wha Ehee, MD,a Ronald M. Witteles, MD,a,b Fatima Rodriguez, MD, MPHd

Atherosclerotic Cardiovascular Disease, Cancer, and Financial Toxicity Among Adults in the United States

Javier Valero-Esponda, MD, MPH,a,b,c Fousad Choonari, BS,a,b Roban Khara, MD, MS,a,b,c Gowtham R. Grandhi, MD, MPH,a Anshul Saxena, PhD,a,b Haider J. Warraich, MD,a,b,c Salim S. Virani, MD, PhD,b,c Nihar R. Desai, MD, MPH,a,b,c Farnam Sanzogohar, PhD, SM, MAsc,a,b,c Harsh M. Khumholz, MD, SM,a,b,c Nestor F. Komiolo, MD, MPH, MBA,a,b,c Khurram Razvi, MD, MPH, MS,a,b,c
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Design</th>
<th>Country</th>
<th>Disease(s)</th>
<th>Treatment</th>
<th>Chemotherapy</th>
<th>Target</th>
<th>Race</th>
<th>% Female Patients</th>
<th>Primary Outcome</th>
<th>Other Notes</th>
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<tr>
<td>Nakama, 2005</td>
<td>RCT</td>
<td>Japan</td>
<td>NHL</td>
<td>CHOP</td>
<td>Vinblastine</td>
<td>No</td>
<td>53%</td>
<td>No Information</td>
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<td>Cardinale, 2006</td>
<td>RCT</td>
<td>Italy</td>
<td>Breast cancer, NHL, myeloma, AML, Ewing's sarcoma</td>
<td>Chemotherapy**</td>
<td>Enalapril</td>
<td>Yes</td>
<td>63%</td>
<td>No Information</td>
<td>None</td>
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<td>Cardinale, 2010</td>
<td>Prospective cohort</td>
<td>Italy</td>
<td>Breast cancer, NHL, leukemia, other</td>
<td>Anthracycline-based therapy</td>
<td>Enalapril or enalapril and carvedilol</td>
<td>Yes</td>
<td>74%</td>
<td>No Information</td>
<td>None</td>
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<tr>
<td>Georgakopoulos et al., 2010</td>
<td>RCT</td>
<td>Greece</td>
<td>NHL and AML</td>
<td>Doxorubicin-based therapy</td>
<td>Enalapril or metoprolol</td>
<td>Yes</td>
<td>45%</td>
<td>No Information</td>
<td>None</td>
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<tr>
<td>Bosch, 2013</td>
<td>RCT</td>
<td>Spain</td>
<td>Leukemia, NHL, and multiple myeloma</td>
<td>Anthracycline** and HDCT</td>
<td>Enalapril and carvedilol</td>
<td>Yes</td>
<td>43%</td>
<td>No Information</td>
<td>None</td>
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<tr>
<td>Keys, 2013</td>
<td>RCT</td>
<td>Turkey</td>
<td>Breast cancer</td>
<td>Anthracycline-based therapy</td>
<td>Nebivolol</td>
<td>Yes</td>
<td>N/A</td>
<td>No Information</td>
<td>None</td>
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<tr>
<td>Guetli, 2016 PRADA</td>
<td>RCT</td>
<td>Norway</td>
<td>Breast cancer</td>
<td>5-fluorouracil, etoposide, and cyclophosphamide</td>
<td>Candesartan or metoprolol sucrose</td>
<td>Yes</td>
<td>N/A</td>
<td>No Information</td>
<td>None</td>
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<tr>
<td>Kaya, 2006</td>
<td>RCT</td>
<td>Turkey</td>
<td>Breast cancer, lymphoma, other</td>
<td>Anthracycline-based therapy</td>
<td>Carvedilol</td>
<td>No</td>
<td>88%</td>
<td>No Information</td>
<td>None</td>
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</tr>
<tr>
<td>Cardinale, 2015</td>
<td>Prospective cohort</td>
<td>Italy</td>
<td>Breast cancer, NHL, myeloma, ovarian, other</td>
<td>Anthracycline-based therapy</td>
<td>Enalapril or enalapril and beta blockers</td>
<td>Yes</td>
<td>74%</td>
<td>No Information</td>
<td>None</td>
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<tr>
<td>Pitskin, 2017 MANTICORE 101</td>
<td>RCT</td>
<td>Canada</td>
<td>HER2 positive breast cancer</td>
<td>Trastuzumab-based therapy</td>
<td>Pertuzumab or bevacizumab</td>
<td>Yes</td>
<td>N/A</td>
<td>No Information</td>
<td>None</td>
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<tr>
<td>Avila, 2018 CEICOY</td>
<td>RCT</td>
<td>Brazil</td>
<td>HER2 negative breast cancer</td>
<td>Doxorubicin, cyclophosphamide, and bevacizumab</td>
<td>Carvedilol</td>
<td>Yes</td>
<td>N/A</td>
<td>No Information</td>
<td>None</td>
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<tr>
<td>Cardinale, 2018 ICOS-ONE</td>
<td>RCT</td>
<td>Italy</td>
<td>Breast cancer, acute</td>
<td>Anthracycline-based therapy</td>
<td>Enalapril</td>
<td>Yes</td>
<td>88%</td>
<td>No Information</td>
<td>None</td>
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<tr>
<td>Guglin, 2019</td>
<td>RCT</td>
<td>United States</td>
<td>HER2 positive breast cancer</td>
<td>Trastuzumab-based therapy</td>
<td>Lisinopril or carvedilol</td>
<td>Yes</td>
<td>N/A</td>
<td>88% white, 7% Black</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
Inequity in Cardio-Oncology: Identifying Disparities in Cardiotoxicity and Links to Cardiac and Cancer Outcomes

Rachel E. Ohman, MD; Eric H. Yang, MD; Melissa L. Abel, MD

Cardioprotective strategies

Baseline health and risk factors → Diagnosis of cancer → Initiation of treatment → Cardiotoxicity surveillance → Cardiotoxicity treatment
• Cardio-oncology is not a niche field…cardiac and cancer disease will be overlapping chronic disease states for many women with survivable cancers
• “Classic” guideline directed medical therapy has minimal/questionable benefits in low-risk patients
• GDMT needs to start immediately if cardiomyopathy develops…to potentially prevent clinical heart failure AND to allow for continued cancer therapies (PERMISSIVE CARDIOTOXICITY)
• Immune checkpoint inhibitors are associated with a rare, but potentially fatal form of myocarditis that responds to high dose steroids in a timely fashion
• Large scale registry/randomized controlled trials needed to evaluate cardioprotective strategies in specific cancer states
• Further work in health disparities is needed to investigate how gaps in care can potentially impact cardiac and cancer outcomes in the cardio-oncology population
Thank You To #bruinhearts In the UCLA Cardio-Oncology Program

- **Class of 2017**
  - Chanaka Wickramasinghe, MD^ (General Cardiology, Eisenhower Desert Cardiology Medical Center)

- **Class of 2018**
  - Vinisha Garg, MD (Interventional Cardiology, Academic Faculty, Loma Linda University Medical Center)
  - Duc Do, MD, MSCR* (Electrophysiology Fellowship, Academic Faculty, UCLA)

- **Class of 2019**
  - Justin Hayase, MD^ (Electrophysiology Fellowship, UCLA, Academic Faculty, Olive View-UCLA)
  - Mirela Tuzovic, MD (Advanced Imaging Fellowship, Academic Faculty, Stanford University)
  - Brian West, MD, MSCR^ (Advanced Imaging Fellowship, UC San Diego, General Cardiology, Sharp Memorial Hospital)

- **Class of 2020**
  - Nikhil Bassi, MD^ (General Cardiology, Hoag Heart and Vascular Center)
  - Sandy Park, MD (General Cardiology, Private Practice, Eisenhower Medical Center)

- **Class of 2021**
  - Dustin Lee, MD (General Cardiology, Academic Faculty, UCLA-Torrance)
  - Heajung Nguyen, MD^ (Electrophysiology Fellowship, UCLA)
  - Ohad Oren, MD (Visiting Heme/Onc Fellow, Mayo Clinic)
    - Cardiology Fellow at MGH, Class of 2024

- **Class of 2022**
  - Manyoo Agarwal, MD (Academic Faculty, Cleveland Clinic-Abu Dhabi, UAE)
  - Yi Lu, MD (General Cardiology, Kaiser-Santa Clara)
  - David Tehrani, MD, MS (Interventional Cardiology, UCLA, University Group, Stanford)

- **Class of 2023**
  - Omid Amidi, MD (General Cardiology, Lakeside Medical Group, Burbank, CA)
  - Christopher Berg, MD^ (General Cardiology, California Heart Associates)
  - Xinjiang Cai, MD, PhD^ (Physician Scientist, UCLA)
  - Elizabeth Hutchins, MD^*
  - Ashley Stein-Merlob, MD** (Physician Scientist, UCLA)

*STAR/Physician Scientist Fellow
^Chief Fellow
• Ronald Reagan-UCLA (Westwood)
  • Eric Yang, M.D.
  • Megan Kamath, M.D. (Cardiomyopathy/MCS/OHT)
  • Gentian Lluri, M.D., Ph.D. (ACHD)
  • Olujimi Ajijola, M.D., Ph.D. (Dysautonomia/EP)
• Santa Monica-UCLA
  • Melkon Hacobian, M.D.
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  • William Finch, M.D.
  • Nidhi Thareja, M.D.
• UCLA-Beverly Hills
  • Pritha Gupta, M.D., Ph.D.
• UCLA-Thousand Oaks, Simi Valley
  • Megha Agarwal, M.D.
• UCLA-Torrance
  • Dustin Lee, M.D.
• UCLA-Encino
  • Boris Arbit, M.D.
• UCLA Housestaff 2022-2023
  • Omid Amidi, MD
  • Christopher Berg, MD
  • Xinjiang Cai, MD, PhD
  • Elizabeth Hutchins, MD
  • Ashley Stein-Merlob, MD
  • Jacqueline Vuong MD
Thank You

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