Monitoring, Diagnosis and Mitigation of Cardiotoxicity

Daniel Lenihan, MD
President, International Cardio-Oncology Society
Presenter Disclosure Information
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• I will not discuss off label use or investigational use in my presentation.

• I have financial relationships to disclose:
  – Research support from: Myocardial Solutions, Inc
  – Consultant (modest): AstraZeneca, BMS, OncXerna, Clementia, Eidos
How/why did Cardio-Oncology get started? Because cardiac safety is a major concern wherever you are.

Increased Risk Of Fatal Side Effects From 3 'Targeted' Cancer Drugs
Medical News Today
Treatment with three relatively new "targeted" cancer drugs has been linked to a slightly elevated chance of fatal side effects, according to a new analysis led by scientists at Dana-Farber Cancer Institute.

http://www.medicalnewstoday.com/releases/241256.php
A population-based study of cardiovascular disease mortality risk in US cancer patients

Kathleen M. Sturgeon, Lei Deng, Shirle Daniel M. Trifiletti, Changchuan Jiang, Scot

1Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA, USA; 2Medicine, Bronx, NY, USA; 3Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL, New York City, NY, USA; 4Division of Cancer Epidemiology and Genetics, National Institutes State Cancer Institute, Hershey, PA, USA

Received 6 December 2018; revised 8 April 2019; editorial decision 8 October 2019; accepted 8 October 2019.

Take home figure Standardized mortality ratios for cancer sites with both ≤30% risk of death from the index-cancer and ≥20% risk of mortality from heart disease were calculated and binned by follow-up time. Cancers sites with at least 1000 person years of risk for death from heart disease between 2000 and 2015 were displayed.
Just look at the developments over the last 45 years.....

Breast Cancer: 45 Years of Research and Progress    Gabriel N. Hortobagyi, MD; https://doi.org/10.1200/JCO.20.00199
Timeline of pivotal events in the development of myeloma therapeutics.

- **1840s**: Case reports Bence Jones protein detected
- **1940s**: Cardinal signs of myeloma reported
- **1960s**: Melphalan + prednisone
- **1980s**: Smoldering myeloma and MGUS identified
- **1990s**: High-dose melphalan, Autologous stem cell transplant, Plerixafor, Bisphosphonates, Thalidomide, Bortezomib, Bortezomib/ doxil, Lenalidomide, Tandem transplant
- **2000s**: Carfilzomib, Pomalidomide, Combinations, Maintenance Rx
- **2010s**: Daratumumab, Elotuzumab, Ixazomib, Panobinostat
- **2015**: CCR Focus
Central Illustration: Priorities Identified for Advancing the Field of Cardio-Oncology

- Clarifying the Role of Cardioprotection
- Personalizing CV Interventions
- Enhancing Survivorship Care
- Building the Community
- Improving CV Outcomes in Stem Cell Transplant
- Managing and Preventing Thromboembolic Events
- Detecting and Treating CV Events with Immunotherapy
- Understanding TKI Cardiotoxicity
- Defining Robust Predictors of Cardiotoxicity


The priorities identified for the discipline of cardio-oncology from the Global Cardio-Oncology Summit 2019 meeting serve as a focus for our collective efforts to advance the field. CV = cardiovascular; TKI = tyrosine kinase inhibitor.
Top 10 Priorities for Cardio-Oncology:

- Knowing the Reproducible Predictors of Cardiotoxicity
- Better define Cardioprotective Strategies in patients with Cancer
- Describe the Optimal Management of Thromboembolic Events in patients with Cancer
- Improve the CV Outcomes in Stem Cell Transplant
- Personalization of Cardiovascular Interventions
MRI Strain can improve detection
PROTECT study, JCO Aug 2019, JCO1900231

Cardioprotection improved survival
### TABLE 5. Cardiovascular Drugs Showing a Prophylactic Effect Against Anthracycline/Trastuzumab-Induced Cardiotoxicity in Adult Cancer Populations

<table>
<thead>
<tr>
<th>STUDY</th>
<th>STUDY DESIGN/ FOLLOW-UP</th>
<th>NO. OF PATIENTS</th>
<th>CANCER TYPE</th>
<th>DRUGS</th>
<th>INTERVENTION</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>Cardinale 2006(^{137})</td>
<td>RCT/12 mo</td>
<td>114</td>
<td>Various</td>
<td>HD CT</td>
<td>Enalapril No LVEF↓; MACE incidence↓</td>
</tr>
<tr>
<td>ARB</td>
<td>Nakamae 2005(^{138})</td>
<td>RCT/7 d</td>
<td>40</td>
<td>NHL</td>
<td>AC</td>
<td>Valsartan No LVEDD↑; no BNP and ANP↑; no QT↑</td>
</tr>
<tr>
<td></td>
<td>Cadeddu 2010(^{139})</td>
<td>RCT/18 mo</td>
<td>49</td>
<td>Various</td>
<td>AC</td>
<td>Telmisartan No peak strain rate↓; no interleukin 6↑</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>Akpek 2015(^{140})</td>
<td>RCT/6 mo</td>
<td>83</td>
<td>Breast cancer</td>
<td>AC</td>
<td>Spironolactone No LVEF↓; no TNI and BNP↑</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Kalay 2006(^{141})</td>
<td>RCT/6 mo</td>
<td>50</td>
<td>Various</td>
<td>AC</td>
<td>Carvedilol No LVEF↓</td>
</tr>
<tr>
<td></td>
<td>Kaya 2013(^{142})</td>
<td>RCT/6 mo</td>
<td>45</td>
<td>Breast cancer</td>
<td>AC</td>
<td>Nebivolol No LVEF and NT-proBNP↑</td>
</tr>
<tr>
<td></td>
<td>Seicean 2013(^{143})</td>
<td>Retrospective/5 y</td>
<td>318</td>
<td>Breast cancer</td>
<td>AC, TRZ</td>
<td>Beta-blockers HF↓</td>
</tr>
<tr>
<td>ACEI + beta-blockers</td>
<td>Bosch 2013(^{144})</td>
<td>RCT/6 mo</td>
<td>90</td>
<td>Hematological</td>
<td>AC</td>
<td>Enalapril + carvedilol No LVEF↓; death↓; HF↓</td>
</tr>
<tr>
<td>Statin</td>
<td>Acar 2011(^{145})</td>
<td>RCT/6 mo</td>
<td>40</td>
<td>Hematological</td>
<td>AC</td>
<td>Atorvastatin No LVEF↓</td>
</tr>
<tr>
<td></td>
<td>Seicean 2012(^{146})</td>
<td>Retrospective/5 y</td>
<td>67</td>
<td>Breast cancer</td>
<td>AC</td>
<td>Statins HF↓</td>
</tr>
</tbody>
</table>

↓, decrease; ↑, increase; ACEI, angiotensin-converting enzyme inhibitor; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; HD CT, high-dose chemotherapy; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; HF, heart failure; MACE, major adverse cardiac events; NHL, non-Hodgkin lymphoma; NT-proBNP, N-terminal-probrain natriuretic peptide; QT, QT interval; RCT, randomized controlled trial; TNI, troponin I; TRZ, trastuzumab.
Top 10 Priorities for Cardio-Oncology:

• Build the Cardio-Oncology Community
• Define and detect the Adverse Cardiac Events in Immunotherapy
• Understanding of Mechanisms of Multi-Targeted Tyrosine Kinase Inhibitors
• Improvements in Survivorship Care
• How do we move forward?
Combination checkpoint inhibitors may have important cardiac effects

Table 1. Incidence of Myocarditis and Myositis in Patients Receiving Nivolumab or Ipilimumab plus Nivolumab.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nivolumab (N = 17,620)</th>
<th>Nivolumab plus Ipilimumab (N = 2974)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any*</td>
<td>10 (0.06)</td>
<td>8 (0.27)</td>
</tr>
<tr>
<td>Fatal events</td>
<td>1 (&lt;0.01)</td>
<td>5 (0.17)</td>
</tr>
<tr>
<td>Myositis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>27 (0.15)</td>
<td>7 (0.24)</td>
</tr>
<tr>
<td>Fatal events</td>
<td>2 (0.01)</td>
<td>1 (0.03)</td>
</tr>
</tbody>
</table>

* The number of patients with myocarditis includes six patients with concurrent myocarditis and myositis.

CENTRAL ILLUSTRATION: Algorithm for Work-Up and Management of Immune-Mediated Myocarditis

Patient on immune checkpoint inhibitors (ICI) or prior ICI use

Patient presenting with new cardiovascular (CV) symptoms

Electrocardiogram (ECG) and troponin test

- Normal results
- Elevated results

- New ventricular arrhythmia or conduction system disease?
  - N: Outpatient echo and NT-proBNP testing
  - Y: Possible myocarditis: Admit patient
    Stop ICI therapy; Urgent Cardiology/Cardio-Oncology consult; Determine whether patient is stable or unstable to dictate treatment

- Elevated troponin/abnormal EKG

- If indeterminate troponin, retest to eliminate false result

CENTRAL ILLUSTRATION: Spectrum of Cardiovascular Toxicities With Immune Checkpoint Inhibitors

Electrical Circuit
- Atrial Fibrillation
- Supraventricular Tachycardia
- Ventricular Tachycardia
- Heart Block

Myocardium
- Myocarditis
- Heart Failure
- Cardiogenic Shock
- Takotsubo Cardiomyopathy

Pericardium
- Pericarditis
- Pericardial Effusion

Vessels
- Coronary Artery Disease
- Temporal Arteritis
- Polymyalgia Rheumatica
- Cerebral Vasculitis
- Hypertension

Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations

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• directoricos@gmail.com