Treatment- and Disease-Related Cardiotoxicity in the Oncology Setting

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Disclosure

- Dr. Durand will not discuss off-label and/or investigational use in his presentation.
- Dr. Durand has nothing to disclose.

Learning Objectives

- Recognize common treatment-related cardiac abnormalities, including appropriate tools for diagnostic evaluation
- List pharmacologic and nonpharmacologic approaches to prevention and management of common cardiac events in cancer patients
- Apply the principles of risk analysis, prevention, early identification of signs and symptoms, and individualized treatment planning for cancer patients at risk of developing disease- or treatment-related cardiac events
- Describe the principles of interprofessional management of cardiac events in cancer patients
Cardiovascular disease is the number 2 killer of cancer survivors

108 million baby boomers will enter the health-care industry by 2015

By 2015 over 15 million US cancer survivors

- Many definitions of a cancer survivor
- Cardiologist viewpoint: Survivorship starts at time of diagnosis (Dr. FitzHugh)

Overview

- Anthracycline-related cardiotoxicity
- QTc prolongation and potential causes
- Tyrosine kinase inhibitors and complications
- Emerging new concepts to consider with cardiotoxicity

Cancer treatment has shifted to targeted therapies, with more than 30 new agents in the past 5 years

- Lifesaving drugs and cardiology approach should support, not interrupt, use
- Limited randomized controlled trials on prevention of cardiotoxicity
- Treatment is based on early detection and prevention of progressive heart failure
Late Mortality Among 5-yr Survivors of Childhood Cancer (CCSS)

N = 20,483

Role of Cancer Treatment in Long-Term Overall and Cardiovascular Mortality After Childhood Cancer

N = 4,122

Classification of Heart Failure (HF)

Examples
ACC/AHA HF stage (Evolution and progression)
NYHA Functional Class (Severity of symptoms)

A: At high risk for developing HF, has a physical abnormality, has a known history of HF, has new-onset or worsening symptoms of HF

I: Asymptomatic

B: Structural disorder of the heart, has prior signs or symptoms of HF

II: HF symptoms with ordinary exertion

C: Underlying structural disorder of the heart, has current or prior symptoms of HF

III: HF symptoms with minimal exertion

D: Advanced structural disorder of the heart, refractory HF, symptoms at rest, despite medical therapy (symptoms despite specialist intervention)

IV: Symptoms at rest
Risk Factors for Heart Failure

- CAD or history of MI
- Hypertension
- Diabetes
- Alcoholism
- Cardiotoxic drugs
- Inherited cardiomyopathies
- Sleep apnea
- Valvular heart disease
- Congenital heart defects
- Other
  - Obesity
  - Age
  - Reduced or falling vital capacity
  - Smoking
  - High or low hematocrit level

CAD = coronary artery disease; MI = myocardial infarction.

Anthracyclines

Doxorubicin Hydrochloride Injection, USP

The probability of developing impaired myocardial function based on a combined index of signs, symptoms, and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m² of doxorubicin, 3 to 5% at a dose of 400 mg/m², 5 to 8% at 450 mg/m², and 6 to 20% at 500 mg/m².


1979: Report by Von Hoff in Ann Intern Med
- Retrospectively reviewed records of 4,018 patients who received doxorubicin
- Definition of doxorubicin-induced CHF:
  - Clinical signs/symptoms of CHF believed to be secondary to doxorubicin by the clinician
  - No routine LVEF assessment!

LVEF = left ventricular ejection fraction; CHF = congestive heart failure.

A More Recent Look at the Data...

Study of 3 anthracycline trials
- Significant event:
  - Symptomatic CHF or
  - EF drop > 20% or
  - EF drop > 10% from normal to below LLN or
  - EF drop > 5% in patients already below LLN
- Almost identical data to what was seen in adjuvant breast cancer studies
  - 7.6% incidence at 240 mg/m²

EF = ejection fraction; LLN = lower limit of normal.

Zinecard (dexrazoxane) package insert
Zinecard (dexrazoxane) package insert

Therapies for Prevention of Cardiotoxicity With Anthracyclines

RPCT-Valsartan for Prevention of Cardiotoxicity

Comparison of LVEF at Baseline and After Chemotherapy

Data expressed as mean values.
N = 90

Overcome Trial (cont)

<table>
<thead>
<tr>
<th>Endpoint +</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature end of the study, n (%)</td>
<td>9 (6-7)</td>
<td>13 (24-2)</td>
</tr>
<tr>
<td>Total mortality, n (%)</td>
<td>9 (6-7)</td>
<td>8 (17-8)</td>
</tr>
<tr>
<td>Death or heart failure, n (%)</td>
<td>9 (6-7)</td>
<td>13 (22-2)</td>
</tr>
<tr>
<td>Death, heart failure or final EF ≤45%, n (%)</td>
<td>9 (6-7)</td>
<td>13 (24-4)</td>
</tr>
<tr>
<td>≥10% decrease in LVF with a final LVF ≤40%, n (%)</td>
<td>2 (4-4)</td>
<td>2 (5-4)</td>
</tr>
<tr>
<td>Heart failure or ≥10% decrease in LVF, n (%)</td>
<td>4 (9-5)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Severe adverse events*, n (%)</td>
<td>9 (20)</td>
<td>15 (33)</td>
</tr>
</tbody>
</table>

*Defined as a serious adverse event that resulted in death or was life-threatening.

N = 90

Which therapies have been demonstrated to prevent development of heart failure with anthracycline-based therapies?

A. Beta blockers JL430
B. Ace-I/ARB JL431
C. Dexrazoxane JL432
D. Atorvastatin JL433
E. Both A and B JL434
F. All of the above JL435
Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy

Daniela Cardinale, MD, Maria T. Santini, MD; Alessandro Colombo, MD; Nicola Colombo, MD; Marcus Buen, MD; Giuseppe Lanzani, MD; Maurizio Civelli, MD; Fabio Pecorelli, MD; Giovanni Martinelli, MD; Cesare Frenzini, MD; Carlo M. Cippolla, MD

- 703 patients (216 males)
- Age 47±12 years
- Treated with high-dose chemotherapy (HDC)
- Poor-prognosis malignancies
- Follow-up = 48 mo
- MACE incidence
  - TnI serum determination
    - Baseline = Before HDC
    - Early = soon after HDC (0, 12, 24, 36, 72 hours)
    - Late = 1 month after HDC
- Follow-up = 48 mo
- MACE incidence


Results

<table>
<thead>
<tr>
<th>TnI Status</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TnI +/+</td>
<td>63 pts (9%)</td>
<td>21%</td>
</tr>
<tr>
<td>TnI +/-</td>
<td>145 pts (21%)</td>
<td>37%</td>
</tr>
<tr>
<td>TnI -/-</td>
<td>495 pts (70%)</td>
<td>84%</td>
</tr>
</tbody>
</table>


Cardiac Events: 3.5-yr Follow-up

- Sudden death
- Cardiac death
- Acute pulmonary edema
- Heart failure
- Asymptomatic ↓ LVEF > 25%
- Life-threatening arrhythmia
- Conduction disturbances requiring pacemaker implantation

* p < .001 vs. TnI -  # p < .001 vs. TnI +/

Cardiac Risk Stratification

- **Persistent TnI+** = High risk
- **Transient TnI+** = Intermediate risk
- **Negative TnI** = Low risk

Positive predictive value = 84%
Negative predictive value = 99%

Troponin I Early Positivity

443 pts
High-dose CT
TnI+ = 114 pts (24%)

- **Enalapril**
- n = 56 pts
- Started 1 month after HDC
- Continued for 1 year
- Physical examination, ECG, ECHO: baseline, 1, 3, 6, 12 mo

Secondary Endpoints: Follow-up 12 mo

<table>
<thead>
<tr>
<th></th>
<th>Total n = 112</th>
<th>ACEI n = 54</th>
<th>Controls n = 58</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>4 (2%)</td>
<td>0 (0%)</td>
<td>4 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart failure</td>
<td>14 (12%)</td>
<td>0 (0%)</td>
<td>14 (22%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Life-threatening arrhythmia</td>
<td>11 (10%)</td>
<td>1 (2%)</td>
<td>10 (16%)</td>
<td>.01</td>
</tr>
<tr>
<td><strong>CUMULATIVE EVENTS</strong></td>
<td><strong>31 (28%)</strong></td>
<td><strong>1 (2%)</strong></td>
<td><strong>30 (52%)</strong></td>
<td><strong>.001</strong></td>
</tr>
</tbody>
</table>
Limited Time to Start Therapy

Responders Have Less Cardiac Event Rates

Heart Failure Specialist Perspective
Continuum of Cancer Intervention:
Lymphoma Patient, R-CHOP

Cycle 1
Baseline ECG
Echo/Strain
Troponin
BNP

Cycle 2
BNP/Troponin
(-) proceed,
(+)
Echo/Strain,
Consider Ace/BB?
Continue Chemo

Cycle 3
BNP/Troponin
(-) proceed,
(+)
Echo/Strain,
Consider Ace/BB?
Continue Chemo

Cycle 4
BNP/Troponin
(-) proceed,
(+)
Echo/Strain,
Consider Ace/BB?
Continue Chemo

ECG HR < 60 (QTC)
Any symptoms
Stop dox LVEF < 40%

Termination of T-wave...In the Eyes of the Beholder

Cancer Patients: Risks for Prolonged QTc

<table>
<thead>
<tr>
<th>ECG</th>
<th>Percent</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged QTc</td>
<td>10.6%</td>
<td>Barbey et al. 2003</td>
</tr>
<tr>
<td>Borderline or prolonged QTc</td>
<td>15%</td>
<td>Vaterasian et al. 2003</td>
</tr>
<tr>
<td>Any ECG anomaly</td>
<td>36%</td>
<td>Barbey et al. 2003</td>
</tr>
</tbody>
</table>

- Molecularly targeted agents with QTc
- Adjuvant regimens, long treatment periods
- *survival = *emphasis toxicity reduction
Drug exposure (Ikr blocker)

Second risk factor
- Bradycardia
- Hypokalemia
- Female gender
- Metabolic inhibitor
- Other QT-prolonging drugs
- Underlying heart disease (CHF, LVH, AF)
- Genetic polymorphism (Ikr or Iks)

More than 25% prolongation of QTc interval from the baseline or a QTc interval longer than 500 ms increases the risk of precipitation of drug-induced torsade de pointes

More than 90% of incidences of drug-induced torsade de pointes occur with QTc values of more than 500 msec

Discontinuation of the offending agent: Any offending agent should be withdrawn. Predisposing conditions such as hypokalemia, hypomagnesemia, and bradycardia should be identified and corrected.

(90% of time, we just stop supportive cast of medications)
Prognosis

Because long QT interval is primarily an electrical disorder, in the absence of structural heart disease and LV dysfunction, the long-term prognosis is good as long as the offending agents and risk factors are corrected and arrhythmia is controlled.

Prognosis

A. Discontinuation of suspected chemotherapy agent JL436
B. Supplementation with potassium and magnesium JL437
C. Discontinuation of supportive medications, antifungals, antiemetics JL438

Which of the following is the most frequent option for treatment of QTc prolongation in patients with cancer?

A. Discontinuation of suspected chemotherapy agent JL436
B. Supplementation with potassium and magnesium JL437
C. Discontinuation of supportive medications, antifungals, antiemetics JL438

Normal Echocardiogram
**Echo vs. MUGA?**

Echo
- Valvular heart disease
- Wall motion abnormalities
- Pulmonary pressures
- Hemodynamics
- Diastology
- Strain

MUGA
- Accurate for low ejection fraction
- Less accurate with rhythm disorders
- No information on valvular disorders
- Little information on wall motion abnormalities

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**Class I Indications: Assessment of LV Function**

- Suspected cardiomyopathy or CHF
- Edema with clinical signs of increased CVP
- Dyspnea or clinical signs of heart disease
- Unexplained hypotension
- Exposure to cardiotoxic agents
- "Pre-chemo"
- Re-evaluation change in status or Rx

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**3D Left Ventricular Function**

[Image of 3D left ventricular function]

MD Anderson Echo Lab Images
Early Detection and Prediction of Cardiotoxicity in Chemotherapy-Treated Patients

Table 4

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% decrease in fractional area at 3 months</td>
<td>74% (71%)</td>
<td>213% (79%)</td>
<td>314% (83%)</td>
<td>322% (83%)</td>
</tr>
<tr>
<td>Elevated EF at 3 months</td>
<td>69% (71%)</td>
<td>263% (82%)</td>
<td>62% (80%)</td>
<td>263% (80%)</td>
</tr>
<tr>
<td>10% decrease in fractional area and elevated EF at 3 months</td>
<td>59% (71%)</td>
<td>331% (87%)</td>
<td>59% (81%)</td>
<td>333% (81%)</td>
</tr>
<tr>
<td>InTol at 3 months</td>
<td>16% (83%)</td>
<td>233% (87%)</td>
<td>13% (83%)</td>
<td>235% (83%)</td>
</tr>
<tr>
<td>10% decrease in fractional area or elevated EF at 3 months</td>
<td>16% (83%)</td>
<td>224% (87%)</td>
<td>12% (83%)</td>
<td>226% (83%)</td>
</tr>
</tbody>
</table>

43 patients exposed to anthracyclines and trastuzumab. EF, BNP, diastolic function did not predict toxicity.


Cardiotoxicity Occurs Earlier Than Change in EF

Doxorubicin was given IV every 3 to 4 weeks. Biopsy specimens were taken approximately 3 weeks following last therapy.

Mean Biopsy Grade

- Mabey — MDW
- Billingham — Stanford
- n=8
- n=18
- n=22
- n=8
- n=3
- n=7

Risk of CHF

Cumulative Doxorubicin Dose (mg/m²)

- <500
- 500-600
- 600-700
- >700

Things to Consider

More than 500 known tyrosine kinases from Human Genome Project
- Over 250 of these tyrosine kinases are cloned and expressed
- 7 tyrosine kinases are FDA approved
- 4 tyrosine kinases targeted (17 kinases in vivo)
- How many kinases in the human genome are cardiac specific?
Kinase-binding profiles of the ABL inhibitors imatinib (upper panel), dasatinib (middle panel), and bosutinib (bottom panel) across a set of protein kinases simultaneously identified from K562 cells. The bars indicate the IC_{50} values, defined as the concentration of drug at which half-maximal competition of kinobead binding is observed.


Any Cardiovascular Toxicity


Hypertension (Grade 2-4)

Decreased LVEF (Grade 2–4)

Drug-Induced HF: FDA-Approved Targeted Cancer Therapies

Drug           Approval  Action              CHF  
Sorafenib      2007      VEGF1,2,3/PDGf  1%    
Dasatinib      2006      BCR-ABL/SRC C-Kit, PDGF  4%    
Sunitinib      2006      VEGF/PDGf/ C-KIT  3%– 14%  
Bevacizumab    2004      VEGF                  2%– 14%  
Trastuzumab    2000      ErbB-2/TKI  3%– 27%  
Imatinib       2001      C-ABL, C-Kit  1%    

CV Mortality Risk Doubles With Each 20/10 mm Hg Increase in BP

BP= blood pressure.
*Individuals aged 40–69 years (N=1 million)
FDA-Approved Targeted Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>HTN/CMP</th>
<th>Responds to ACE/BB</th>
<th>SHF/DHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>CMP</td>
<td>Yes</td>
<td>SHF</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>CMP</td>
<td>Yes</td>
<td>SHF</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>HTN/CMP</td>
<td>Yes</td>
<td>SHF/DHF</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>HTN/CMP</td>
<td>Yes</td>
<td>SHF/DHF</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>CMP</td>
<td>Yes</td>
<td>SHF</td>
</tr>
<tr>
<td>Imatinib</td>
<td>CMP</td>
<td>Yes</td>
<td>SHF</td>
</tr>
</tbody>
</table>

Stanford study of 247 consecutive patients referred to Cardio-Oncology clinic.
- 79 patients with treatment-emergent LVEF drops
  - Average LVEF drop: 60% → 41%
- Cardiac interventions:
  - B-blockers: 84%
  - ACEi or ARB: 63%
  - CRT for 4 patients: Dramatic improvements for all 4
- Average LVEF post-intervention: 53%
  - 77% recovered LVEF to normal
  - 76% able to continue/complete planned cancer therapy

A “Real World” Example

Hypertension Is a Biomarker of Efficacy in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib

## Clinical Outcome by Hypertension Status

<table>
<thead>
<tr>
<th></th>
<th>Max. SBP ≥ 140 mm Hg (n = 441)</th>
<th>Max. SBP &lt; 140 mm Hg (n = 93)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response, n (%)</td>
<td>241 (54.6%)</td>
<td>9 (9.7%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Progression-free survival, months</td>
<td>12.5</td>
<td>2.5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Overall survival, months</td>
<td>30.5</td>
<td>7.8</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

## Median OS by Use of Anti-HTN Agents, HTN-Induced Dose Reductions and HTN Status as Defined by Maximum SBP ≥ 140 mm Hg on Sunitinib

### Median OS by Use of Anti-HTN Agents, HTN-Induced Dose Reductions and HTN Status as Defined by Maximum SBP ≥ 140 mm Hg on Sunitinib

<table>
<thead>
<tr>
<th></th>
<th>Max. DBP ≥ 90 mm Hg (n = 352)</th>
<th>Max. DBP &lt; 90 mm Hg (n = 172)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response, n (%)</td>
<td>207 (57.2%)</td>
<td>43 (25.0%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Progression-free survival, months</td>
<td>13.4</td>
<td>5.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Overall survival, months</td>
<td>32.1</td>
<td>15.0</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

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**Binding to specific adrenergic receptors, β-blockers inhibit cancer cell migration and metastasis, suggesting a novel targeted therapeutic application in protecting against breast cancer disease progression**

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Baseline Hypertensive BC Patients Treated With Beta Blockers Live Longer

![Graphs showing survival rates for baseline hypertensive BC patients treated with beta blockers compared to untreated patients.](image)

Figure 1a: Hypertensive BC patients who spontaneously started beta-blockers showed significantly (p=0.02) longer times before going into sepsis compared to those not treated.

Figure 1b: Hypertensive BC patients receiving beta-blocker therapy showed significantly (p=0.041) improved 16-year survival rates compared to non-treated patients.

Which of the following is true?

A. Anthracycline cardiotoxicity is an irreversible process and leads to progressive heart failure and death JL439

B. Tyrosine kinase-related cardiomyopathy is an irreversible cardiomyopathy JL440

C. QTc prolongation of any kind requires discontinuation of chemotherapy indefinitely JL441

D. None of the above is true JL442
Heart Success

Organizations for the future
- Conquer, MD Anderson Cancer Center, 2001
- Cardiology Oncology Partnership Vanderbilt USA, 2004
- International CardiOncology Society, Milan, Italy, 2009
- Brazilian Cardiology Oncology, Sao Paulo, Brazil, 2009
- Canadian CardiOncology, 2010

Ongoing Studies

- Enalapril with chemo vs. troponin-I guided strategy
  - NCT01968200, Italy
- Candesartan vs. placebo during/after trastuzumab
  - NCT00459771, Netherlands
- Carvedilol vs. placebo during anthracycline-based breast cancer therapy
  - NCT01724460, Brazil
- Carvedilol CR vs. lisinopril vs. placebo during trastuzumab Rx
  - NCT01016886, Canada
- Bisoprolol vs. perindopril vs. placebo during trastuzumab Rx
  - NCT01009918, USA
- Metoprolol vs. candesartan vs. placebo during Breast CA Rx
  - NCT01434134, Norway

Carvedilol Dose-Response Trial (MOCHA*)
Effect on Ejection Fraction and Mortality

Patients receiving diuretics, ACE inhibitors, ± digoxin; follow-up 6 months; placebo (n=84), carvedilol (n = 261).

Carvedilol

Changes in LVEF

- Placebo
- 6.25 mg bid
- 12.5 mg bid
- 25 mg bid

*p < .05 vs. placebo

Conclusions

- Cardiologists and oncologists must collaborate
- Exciting new cancer therapies are being discovered; however, in order to maximize their potential, cardiac toxicities need to be identified and addressed upfront
- Although recent clinical experience has shown significant cardiotoxicity post trial with cancer therapies, we have also seen resolution of toxicity using evidence-based cardiology guidelines (beta blockers need further study)
- More collaborative work with biomarkers/cardiac imaging for early detection and treatment

Thank you!

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