Cardio-Oncology: Advancing Cardiovascular Care of the Oncology Patient

Vijay U. Rao, MD, PhD, FACC, FASE
Franciscan Physician Network
Indiana Heart Physicians
Director, Franciscan Health
Inpatient Heart Failure, Anti-Coagulation Clinic, Cardiac Research and Cardio-Oncology Clinic
Presenter Disclosure Information
Cardio-Oncology: Advancing Cardiovascular Care of the Oncology Patient
Vijay Rao, MD, PhD, FACC, FASE

- I am on the speaker’s bureau for BMS/Pfizer, Daichi-Sankyo, Novartis
- I am a consultant to CryoLife
- I will not discuss off label or investigational use in my presentation.
Objectives

1. Recognize the growing burden of cardiotoxicity from newer chemotherapeutic agents.
2. Review treatment options for patients with cardiotoxicity due to anthracyclines, radiation, and newer agents such as tyrosine kinase inhibitors (TKIs).
3. Appreciate the role of pertinent clinical follow-up for patients who have completed chemotherapy and radiation therapy.
2010 CDC US Mortality Data

Causes of death

- Heart disease
- Cancer
- Chronic lower respiratory diseases
- Stroke
- Unintentional injuries
- Alzheimer's disease
- Diabetes
- Nephritis, nephrotic syndrome, and nephrosis
- Influenza and pneumonia
- Suicide

No. of deaths (in thousands)
Hey, how am I supposed to hear his request for new drug approval with all your screaming?
Anthracycline Dose Cardiac Toxicity

Anthracycline Cardiotoxicity

Acute cardiotoxicity

Acute toxic myocarditis with myocyte damage (pyknotic debris) and inflammatory infiltrate

Chronic cardiotoxicity

Cardiomyopathy with shrunken myocytes with myofibrillar loss and with sacrotubular distension

Myofibrillar loss with Z-band remnants

Swollen, dilated sarcotubules

Anthracycline Cardiotoxicity

Predictors

- Anthracycline cumulative dose:
  - Doxorubicin $>240 \text{ mg/m}^2$
  - Epirubicin $>500 \text{ mg/m}^2$

- Anthracycline type and rate of administration

- Mediastinal radiation

- Age (<15 or >65 yrs)

- Female gender

- Pre-existing CVD

- Hypertension

Ewer MS and Ewer SM. Nat. Rev. Cardiol. 2010; 7, 564–75
# Cardiotoxicity Classification System

## Type I
- Anthracycline
- Acute (within 1 week) vs. chronic (late onset)
- Cumulative dose effect
- High probability of recurrent dysfunction

## Type II
- Herceptin® (Traztuzumab), Bevacizumab
- High likelihood of recovery
- Not dose related
- Increasing evidence for the relative safety of re-challenge
Cardio-toxicities of Molecular Targeted Therapies

- Acute Coronary Syndromes
- QT prolongation
- Hypertension
- Left ventricular systolic dysfunction
- Heart Failure

ANTI-ANGIOGENIC VEGF targeting (VEGF mAB, oral VEGFR inhibitors)
- SIGNAL TRANSDUCTION INHIBITORS
- HER Family (HER2 mAB or TkI)
  - PKC inhibitors
  - Farnesyl transferase inhibitors
  - PDGFR, c-kit and ABL inhibitors

ANTI-ANGIOGENIC VEGF targeting (VEGF mAB, oral VEGFR inhibitors)
- HER Family (HER2 mAB or TkI)
HER2 Pathway Inhibitors (HER2-Is)

Murphy CG and Morris PG. Anti-Cancer Drugs 2012, 23:765–76
Identifying Cardiotoxicity

- History and Physical
- ECG
- Labs: Troponin, BNP
- Imaging:
  - MUGA
    - Reproducible
    - Radiation Exposure
  - ECHO
    - Ejection Fraction (2D/3D)
    - Global Longitudinal Strain (GLS)
    - Assess for pericardial effusions/valvular disease
- Cardiac MRI, gold standard for assessment of LV function
Echocardiography and Myocardial strain analysis

10% drop in GLS predicts future drop in EF for both anthracycline and Herceptin chemotherapy
Pharmacologic Treatment

- Ace-Inhibitors
- Beta-blockers (carvedilol, nebivolol)
- Statins
- Dexrazoxane
ACE Inhibitor Therapy

Percent recovering (LVEF increase ≥15%)

With ACE-inhibition: 88% (7/8)

P < 0.0001

Without ACE-inhibition: 8% (1/33)

Months after cardiotoxic decline or start of ACE-inhibition

Response to Therapy

Critical Dependence on Time

Cardinale D et al. JACC 2010, 55:213-20
**Herceptin Cardiotoxicity**

![Bar chart showing mean LVEF (%) for different scenarios.](chart)

- **Prior to trastuzumab therapy (n=38)**
- **Following trastuzumab therapy (n=38)**
- **Following standard therapy for heart failure (n=32) or observation (n=6)**
- **Following trastuzumab rechallenge (n=25; all on standard therapy)**

Ewer MS et al. J Clin Oncol 2005;23:7820-6
Qtc Prolongation

- Dreaded lethal arrhythmia: torsades de pointes
- Histone Deactylases, Multi-targeted TKIs, Src/Abl kinase inhibitors, Protein Kinase C inhibitors
- Correct K and Mag prior to starting agents, followed with ECG, avoid other Qtc prolonging agents (anti-psychotics, anti-depressants, antibiotics, anti-fungals, anti-emetics, methadone)
Angiogenesis Inhibitors and HTN

- Tyrosine Kinase Inhibitors (TKIs), 15-60% develop HTN
- Thought due to increased peripheral vascular resistance due to decreased endothelial nitric oxide synthetase (eNOS) (no relationship seen with humoral factors or volume expansion) Ann Oncol (2007) 18 (6): 1121-1122.
- Sorafenib, Bevacizumab, Sunitinib
- Treatment: RAS inhibitor and possible nebivolol or isosorbide dinitrate; avoid inhibitors of CYP3A4 (diltiazem, verapamil) as TKIs are substrates
Radiation Therapy

- Adjuvant therapy in breast cancer, Hodgkin’s lymphoma, lung cancer
- Cardiac complications when dose is greater than 30 Gy
- Shrinking problem: breath holding technique, smaller fractions, PET scans
Radiation Induced Cardiotoxicity

Valve disease

Atherosclerosis
(Symptomatic or asymptomatic)

Pericardial disease
(Acute pericarditis; chronic pericarditis; pericardial effusion; constrictive pericarditis)

Myocardial and endocardial disease
(Pancarditis, cardiomyopathy)

Conduction disturbances
(Right bundle branch block, atrioventricular block)
5-FU (family) and coronary vasospasm

- 1.27-18% reported incidence
- Single agent or combination therapy, seen more often with bolus dosing vs continuous infusions
- Usually seen after a few days of therapy
- ST elevation that may or may not be associated with a discrete lesion; also occurs with 2nd generation agents (e.g., Capecitabine)
- Try to use different agent if possible, if not, trial of isosorbide mononitrate and/or Nifedipine (both of which are used to treat coronary vasospasm) and then re-challenge at lower dose
Case Study

- 57 yo male with hx of B cell lymphoma
- Treated with R-CHOP 6 cycles (total dose of doxorubicin >400mg/m2, XRT >40Gy)
- Pre-treatment LVEF >55%
- Post-treatment LVEF 45%, strain -15%
- Fatigue, mild dyspnea, no chest pain
- ? etiology
Case Study

- Stress testing shows ischemia in inferiorlateral territory
- Cath with complete total occlusion of right coronary artery, received drug eluting stent
- Dual anti-platelet therapy, BB, statin
- While treatment with doxorubicin and XRT put him at risk for cardiotoxicity, CAD remains the #1 cause of LV systolic dysfunction
What is the role of the CardioOncology Clinic?

- Increase communication between oncologists and cardiologists
- Identify high risk patients prior to chemotherapy (CV risk score) and optimize risk factors
- Implement cardiotoxicity monitoring algorithms
- Initiate CV protective therapies
- Establish appropriate follow-up once chemotherapy is completed
Consensus Statements

- SCAI Expert Consensus Statement: Evaluation, Management, and Special Considerations of Cardio-Oncology Patients in the Cardiac Catheterization Laboratory. Cezar A. Illiescu, MD, FSCAI, FACC, Cindy L. Grines, MD, FSCAI, FACC, Joerg Herrmann, MD, Eric H. Yang, MD, FACC, Mehmet Cilingiroglu, MD, FSCAI, FESC, FACC, Konstantinos Charitakis, MD, FACC, Abdul Hakeem, MD, FSCAI, FACC, Konstantinos P. Toutouzas, MD, FSCAI, FESC, Massoud A. Leesar, MD, and Konstantinos Marmagkiolis, MD, FSCAI, FACC.

- Catheterization and Cardiovascular Interventions 00:00–00 (2015)


References

Berry GJ, Jorden M. Pediatr Blood & Vancer 2005;44:630-7
Ewer MS and Ewer SM. Nat. Rev. Cardiol. 2010; 7,564–75
Murphy CG and Morris PG. Anti-Cancer Drugs 2012, 23:765–76
Cardinale D et al. JACC 2010,55:213-20
Ewer MS et al. J Clin Oncol 2005;23:7820-6

SCAI Expert Consensus Statement: Evaluation, Management, and Special Considerations of Cardio-Oncology Patients in the Cardiac Catheterization Laboratory Cezar A. Iliescu,1 MD, FSCAI, FACC, Cindy L. Grines,2 MD, FSCAI, FACC, Joerg Herrmann,3 MD, Eric H. Yang,4 MD, FACC, Mehmet Cilingiroglu,5,6 MD, FSCAI, FESC, FACC, Konstantinos Charitakis,7 MD, FACC, Abdul Hakeem,8 MD, FSCAI, FACC, Konstantinos P. Toutouzas,9 MD, FSCAI, FESC, Massoud A. Leesar,10 MD, and Konstantinos Marmagkiolis,11,12* MD, FSCAI, FACC Catheterization and Cardiovascular Interventions 00:00–00 (2015)


Yeh E, Bickford CL JACC 2009, 53:2231-47
Email:
Vijay.Rao@franciscanalliance.org
For more information
<table>
<thead>
<tr>
<th>Medication-related risk</th>
<th>Patient-related risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High (risk score 4):</strong></td>
<td>• Cardiomyopathy or heart failure</td>
</tr>
<tr>
<td>Anthracyclines, Cyclophosphamide,</td>
<td>• CAD or equivalent (incl. PAD)</td>
</tr>
<tr>
<td>Ifosfamide, Clofarabine, Herceptin</td>
<td>• HTN</td>
</tr>
<tr>
<td><strong>Intermediate (risk score 2):</strong></td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>Docetaxel, Pertuzumab, Sunitinib,</td>
<td>• Prior or concurrent anthracycline</td>
</tr>
<tr>
<td>Soratinib, Sorafenib</td>
<td>• Prior or concurrent chest radiation</td>
</tr>
<tr>
<td><strong>Low (risk score 1):</strong></td>
<td>• Age &lt;15 or &gt;65 years</td>
</tr>
<tr>
<td>Bevacizumab, Dasatinib, Imatinib,</td>
<td>• Female gender</td>
</tr>
<tr>
<td>Lapatinib</td>
<td></td>
</tr>
<tr>
<td><strong>Rare (risk score 0):</strong></td>
<td></td>
</tr>
<tr>
<td>For example, Etoposide, Rituximab,</td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td></td>
</tr>
</tbody>
</table>

**Overall risk by Cardiotoxicity Risk Score (CRS)**
(risk categories by drug-related risk score plus number of patient-related risk factors:
CRS >6: very high, 5-6: high, 3-4: intermediate, 1-2: low, 0: very low)

2. Monitoring recommendations

**Very high cardiotoxicity risk:**  TTE with strain before every (other) cycle, end, 3-6 months and 1 year, optional ECG, cTn with TTE during chemotherapy

**High cardiotoxicity risk:** TTE with strain every 3 cycles, end, 3-6 months and 1 year after chemotherapy, optional ECG, cTn with TTE during chemotherapy

**Intermediate cardiotoxicity risk:** TTE with strain, mid-term, end and 3-6 months after chemotherapy, optional ECG, cTn mid-term of chemotherapy

**Low cardiotoxicity risk:** Optional TTE with strain and/or ECG, cTn at the end of chemotherapy

**Very low cardiotoxicity risk:** None

3. Management recommendations

**Very high cardiotoxicity risk:** Initiate ACE-I/ARB, Carvedilol, and statins, starting at lowest dose and start chemotherapy in 1 week from initiation to allow steady state, up-titrate as tolerated

**High cardiotoxicity risk:** Initiate ACE-I/ARB, Carvedilol, and/or statins

**Intermediate cardiotoxicity risk:** Discuss risk and benefit of medications

**Low cardiotoxicity risk:** None, monitoring only

**Very low cardiotoxicity risk:** None, monitoring only

Tests: TTE with strain, EKG, cTn
Oncology/hematology patient

Before treatment

Cardiovascular review (incl. history, examination, CXR, ECG, and echocardiogram with strain)

Cardiovascular risk?

Cardiomyopathy (incl. abn strain)
Heart failure (incl. abn CXR)
CAD or equivalent (incl. abn ECG)
HTN (esp. uncontrolled, end-organ signs)
Arrhythmias/syncope
QTc prolongation >500 ms
For cardiotoxic drugs, esp. anthracyclines, the following factors add to the risk:
Age <15 or >65 years
Female gender

Cardio-oncology consultation

During treatment

Cardiovascular complications?

Decline in ejection fraction
Myocardial strain abnormality
Heart failure (incl. abn CXR)
Pericardial effusion
Cardiac biomarker elevation
Myocardial ischemia
Arrhythmias
QTc prolongation >500 ms
Syncope
Hypotension
Uncontrolled hypertension

Cardio-oncology consultation

After treatment

Cardiovascular complications?

Any CV abnormality noted in f/u or Doxorubicin ≥240 mg/m²
Radiation ≥30 Gy
Radiation + anthracycline or high-dose cyclophosphamide, esp. if strenuous activity or pregnancy is planned

Cardio-oncology consultation