CardioOncology: The Promise and Pitfalls of Personalized Medicine

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Presenter Disclosure Information
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- I am on the speaker’s bureau for BMS/Pfizer, Boehringer-Ingelheim/Lilly, Novartis
- I will not discuss off label or investigational use in my presentation.
Goals & Objectives

- Recognize the growing burden of cardiotoxicity from new chemotherapeutic agents
- Analyze screening algorithms and risk scores for cardiotoxicity
- Recognize potential cardiovascular complications of novel molecular targeted therapies, including arrhythmias, cardiomyopathy, cardiac ischemia and hypertension
Outline

- CardioOncology: Historical perspective
- Radiation therapy and CV disease
- Anti-Metabolite Coronary Vasospasm
- Molecular Targeted Therapies (Precision Medicine)
  - Trastuzumab (Herceptin®)
  - Tyrosine Kinase Inhibitors (TKIs)
  - Checkpoint Inhibitors
2015 CDC US Mortality Data

Causes of Death

- Heart Disease
- Cancer
- Chronic Lower Respiratory Diseases
- Accidents
- Stroke
- Alzheimer's Disease
- Diabetes
- Influenza and Pneumonia
- Kidney Disease
- Suicide

# of Deaths

0 100,000 200,000 300,000 400,000 500,000 600,000 700,000
**Cardiac Disease is very likely to coexist with a diagnosis of cancer**

**Table 1. Causes of Death Within 10 Years of Diagnosis in Women With Breast Cancer**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Age (years)</th>
<th>&lt;45</th>
<th>%</th>
<th>45-54</th>
<th>%</th>
<th>55-64</th>
<th>%</th>
<th>65-74</th>
<th>%</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td></td>
<td>226</td>
<td>95.0</td>
<td>307</td>
<td>82.4</td>
<td>312</td>
<td>62.5</td>
<td>313</td>
<td>44.5</td>
<td>1,188</td>
<td>64.2</td>
</tr>
<tr>
<td>Circulatory system disorder</td>
<td></td>
<td>1</td>
<td>0.4</td>
<td>10</td>
<td>2.5</td>
<td>52</td>
<td>10.4</td>
<td>169</td>
<td>24.0</td>
<td>232</td>
<td>12.5</td>
</tr>
<tr>
<td>Other cancer</td>
<td></td>
<td>5</td>
<td>2.1</td>
<td>30</td>
<td>7.3</td>
<td>74</td>
<td>14.8</td>
<td>105</td>
<td>14.9</td>
<td>214</td>
<td>11.6</td>
</tr>
<tr>
<td>Other cause</td>
<td></td>
<td>6</td>
<td>2.5</td>
<td>32</td>
<td>7.8</td>
<td>61</td>
<td>12.2</td>
<td>116</td>
<td>16.5</td>
<td>215</td>
<td>11.6</td>
</tr>
<tr>
<td>Total No. of deaths</td>
<td></td>
<td>238</td>
<td>100.0</td>
<td>409</td>
<td>100.0</td>
<td>499</td>
<td>100.0</td>
<td>703</td>
<td>100.0</td>
<td>1,849</td>
<td>100.0</td>
</tr>
<tr>
<td>Total No. of patients</td>
<td></td>
<td>1,678</td>
<td>100.0</td>
<td>3,725</td>
<td>100.0</td>
<td>4,253</td>
<td>100.0</td>
<td>3,194</td>
<td>100.0</td>
<td>12,850</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Younger than 75 years of age, diagnosed between 1990 and 2006.*

Colzani, et al JCO 2011 29:p 4014-21
Hey, how am I supposed to hear his request for new drug approval with all your screaming?
“One of the goals of cardio-oncology is to prevent the cancer survivor of today from becoming the heart failure patient of tomorrow.”
Number of PUBMED articles on Cardio-Oncology

1971

2014
Cardio-oncology service

- Monitoring for early cardiotoxicity
- Secondary prevention of cardiotoxicity
- Investigation of suspected cardiac invasion by tumour
- Pre-operative assessment for cancer surgery
- Management of other cardiovascular toxicity e.g. hypertension
- Primary prevention of cardiotoxicity in high-risk patients
Anthracyclines

- In the 1950s, daunorubicin, a compound isolated from the soil bacterium *Streptomyces peucetius*, was found effective against tumors in mice, and eventually, acute leukemia and lymphoma.

- Among the most effective anticancer treatments ever developed and are effective against more types of cancer than any other class of chemotherapeutic agents

- MOA: intercalates between DNA/RNA, affects topoisomerase II, free radical generation
  - Associated with troubling side-effect: cardiotoxicity (often irreversible)
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 mg/m²
  - Epirubicin >500 mg/m²

- 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
Clinical Uses for Radiation Therapy

- Therapeutic radiation serves two major functions
  - To cure cancer
    - Destroy tumors that have not spread
    - Kill residual microscopic disease left after surgery or chemotherapy
  - To reduce or palliate symptoms
    - Shrink tumors affecting quality of life, e.g., a lung tumor causing shortness of breath
    - Alleviate pain or neurologic symptoms by reducing the size of a tumor

External beam radiation treatments are usually scheduled five days a week and continue for one to ten weeks.
Radiation Therapy

- Mantle Cell, Adjuvant therapy in breast cancer, Hodgkin’s lymphoma, lung cancer
- Cardiac complications when dose is greater than 30 Gy
- Shrinking problem: breath holding technique, shielding, 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)
Anti-Metabolite (5-FU): Coronary Vasospasm

- 5-FU (Fluorouracil®), Capecitabine (Xeloda®), Gemcitabine (Gemzar®): prevent DNA replication by inhibiting thymidylate synthetase
- Used to treat breast, colorectal, pancreatic, skin cancers
- Up to 2-5% of patients develop chest pain and ST elevation with coronary vasospasm (usually within 72 h of continuous infusion) and can be lethal
- Occurs less often with bolus dosing
- Occurs more often if patient with pre-existing CV disease
- Can consider re-challenge with nitrate/ccb
- Reversal agent (Vista-guard®) is available but very expensive
Variations in $DPYD$ can lead to DPD insufficiency.

This results in an inability to inactivate 5-FU leading to increased levels of active drug in the system that can result in toxicity.
Chemotherapy vs Targeted Therapy

- **Chemotherapy:**
  - Drugs that effect cells that are doubling
  - Not very specific
  - Mostly intravenous, some oral agents
  - Cytotoxic

- **Targeted therapy:**
  - Drugs that inhibit a more specific target in cells
  - Many are oral agents
  - Mixture of cytostatic and cytotoxic
Targeted Cancer Therapy

1. Molecular Profiling
   - Markers predictive of drug sensitivity/resistance
2. Prognostic Markers
   - Markers predictive of adverse events
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
Herceptin Has Altered The Natural History of HER2+ Breast Cancer

Stage IV Breast Cancer – Overall Survival

<table>
<thead>
<tr>
<th>HER2 Status</th>
<th>1-Year</th>
<th>2-Year</th>
<th>5-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-negative, No Herceptin</td>
<td>75.1%</td>
<td>54.9%</td>
<td>24.5%</td>
</tr>
<tr>
<td>HER2-positive, No Herceptin</td>
<td>70.2%</td>
<td>41.3%</td>
<td>13.2%</td>
</tr>
<tr>
<td>HER2-positive, With Herceptin</td>
<td>86.6%</td>
<td>63.2%</td>
<td>23.4%</td>
</tr>
</tbody>
</table>

Dawood S et al, American Society of Clinical Oncology, June 2008
©2009 Genentech - 2009 Investment Community Meeting
HER2 Pathway Inhibitors (HER2-Is)

Murphy CG and Morris PG. Anti-Cancer Drugs 2012, 23:765–76
<table>
<thead>
<tr>
<th>Cumulative Incidence (%)</th>
<th>Year After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>1.2</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>3.6</td>
</tr>
<tr>
<td>Anthracycline +</td>
<td>6.2</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td></td>
</tr>
<tr>
<td>Other agents</td>
<td>1.3</td>
</tr>
<tr>
<td>None</td>
<td>0.9</td>
</tr>
</tbody>
</table>

(Reproduced, with permission, from Journal of the National Cancer Institute 2012;104:1293-1305.)
Herceptin Cardiotoxicity

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
Echocardiography

- Apex of heart
- RY, LY
- TV, AV, MV
- RA, LA
- Septum
- Papillary muscles
- Tricuspid valve
- Aortic valve
- Right atrium
- Interatrial septum
- Mitral valve
- Left atrium
Myocardial strain analysis

10% drop in GLS predicts future drop in EF for both anthracycline and trastuzumab chemotherapy
Cardiac MRI

Aorta

Location of magnetic resonance imaging section

Left ventricle

Right ventricle (RV)

3D angiogram of heart

Normal left ventricle

Damaged left ventricle from heart attack

Left ventricle not receiving enough blood
Pharmacologic Treatment for Anthracycline and Trastuzumab Cardiotoxicity

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

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

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

P < 0.0001

13:699-709
Response to Therapy
Critical Dependence on Time

Cardinale D et al. JACC 2010, 55:213-20
Response to Therapy and Outcome

Cardinale D et al. JACC 2010,55:213-20
GLEEVEC (Imatinib)

- Molecular consequence of the t(9;22) is the fusion protein BCR–ABL, which has increased in tyrosine kinase activity.
- BCR-ABL protein transform hematopoietic cells so that their growth and survival become independent of cytokines.
- It protects hematopoietic cells from programmed cell death (apoptosis).
Dasatinib SPRYCEL®

Mechanism of action

- Bind to the **inactive** and **active** conformation of the ABL-kinase domain

- **Greater affinity** to the Abl-kinase domain compared to Imatinib

- Activity **against several Abl-kinase mutation**

# Late Toxicities

**Dasatinib – associated with pulmonary hypertension**[^a]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Any CV condition n = 43</th>
<th>No CV condition n = 216</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid retention</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>Superficial edema</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>23</td>
<td>7</td>
</tr>
</tbody>
</table>

**Nilotinib – peripheral arterial occlusive disease (PAOD)**[^b]

<table>
<thead>
<tr>
<th></th>
<th>No TKIs, n = 533</th>
<th>Nilotinib only, n = 556</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PAOD cases</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Cumulative incidence, %</td>
<td>0.6</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Angiogenesis Inhibitors: HTN

- **Drugs:** Sorafenib (VEGFR, PDGFR and Raf family kinases), Bevacizumab (VEGFR), Sunitinib (VEGFR, PDGFR)
- **Prevalence:** 15-60% develop HTN
- **Mechanism:** 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.
- **Treatment:** Ace-Inhibitors and/or dihydropyridine calcium channel blockers; avoid inhibitors of CYP3A4 (diltiazem, verapamil) as TKIs are substrates, could consider nevibolol (Bystolic) (only beta-blocker which increases NO bioavailability)
- May need to decrease dose or halt therapy until HTN controlled; HTN resolves once agent stopped
## VEGF1-Induced Hypertension Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>NOT Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of HTN</td>
<td>BMI</td>
</tr>
<tr>
<td>&gt;1 VEGF1 combination therapy</td>
<td>Race</td>
</tr>
<tr>
<td>&gt;65 years of age</td>
<td>Renal function</td>
</tr>
<tr>
<td>Smoking</td>
<td>Family history of HTN or CVD</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td></td>
</tr>
</tbody>
</table>
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
A Virtuous Circle

Cancer sabotages steps in the immune cycle where T-cells are normally armed, aimed, and unleashed to kill tumors. Below are the places companies’ planned drugs intervene.

Multiple targets in immuno-oncology

1. Release of cancer cell antigens
   - AstraZeneca
   - Celldex
   - Merck KGaA
   - Roche

2. Cancer antigen presentation
   - AstraZeneca
   - Celldex
   - Merck
   - Roche

3. Priming and activation
   - Agenus
   - AstraZeneca
   - Bristol-Myers
   - Celldex
   - Incyte
   - Merck
   - Pfizer
   - Roche

4. Trafficking of T-cells to tumors

5. Infiltration of T-cells into tumors
   - Roche
   - Lilly

6. Recognition of cancer cells by T-cells
   - Bluebird/Celgene
   - Juno
   - Kite
   - Novartis
   - Roche

7. Killing of cancer cells
   - AstraZeneca
   - Bristol-Myers
   - Celgene
   - Five Prime
   - Incyte

Sources: Roche, Credit Suisse, company reports
Illustration: Carl Winters for Barron’s
Checkpoint Inhibitors [Ipilimumab (Yervoy)/Nivolumab (Opdivo)]
1:400 patients estimated to develop myocarditis
CardioOncology Clinic

- Increase awareness about topic and clinical considerations among PCPs and cardiologists
- Increase access to subspecialty expertise (telemedicine initiative)
- Contribute to research in the field
  - Incorporating standard CV risk prediction tools in cardio-onc setting
  - TKI-HTN grant
  - SURVIVE registry (10 sites globally)
References

- Cardiovascular Toxic Effects of Targeted Cancer Therapies
  Javid J. Moslehi, M.D.

- SCAI Expert Consensus Statement: Evaluation, Management, and Special Considerations of Cardio-Oncology Patients in the Cardiac Catheterization Laboratory Iliescu et al.
  Catheterization and Cardiovascular Interventions 00:00–00 (2015)