Clinician’s Perspective: Best practices for cardiac safety monitoring in oncology clinical trials

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The big C

Drugs in development*, 2010

- Cancer
- Central nervous system
- Infections
- Pain and inflammation
- Cardiovascular
- Diabetes and metabolism
- Gastrointestinal
- Respiratory
- Blood disorders
- Dermatological

*Top ten therapeutic areas for the world’s big pharmaceutical firms, includes drugs in Phase I, II, III or awaiting FDA approval

Source: Medco, R&D Directions

Estimated Number of Cancer Survivors in the US

Projections

Cardiovascular Side Effects of Modern Cancer Therapy

- Arrhythmia
- Cardiac Dysfunction
- Heart Failure
- Hypertension
- Thromboembolism
- AP / MI
Developing a Cardiology-Oncology Partnership
Oncology Drug Development
Cardiac Safety Monitoring in Clinical Trials
Lessons Learned!
Cardiotoxicity Associated with Trastuzumab

- Metastatic BC (AC= doxorubicin + cyclophosphamide)

<table>
<thead>
<tr>
<th>Cardiotoxicity</th>
<th>Trastuzumab + AC (N=143)</th>
<th>AC (N=135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac dysfunction %</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>NYHA III/IV CHF, %</td>
<td>19</td>
<td>3</td>
</tr>
</tbody>
</table>


Subsequent trials in Early Breast Cancer

- Stringent CV eligibility criteria
- Changes in administration
- Cardiac monitoring schema

NEW ERA OF CARDIAC MONITORING IN ONCOLOGY TRIALS
# Cardiotoxicity in Early HER2+ Breast Cancer Trials

<table>
<thead>
<tr>
<th>1 year of Herceptin</th>
<th>n</th>
<th>Asymptomatic decline in LVEF, %</th>
<th>Severe HF, %</th>
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</thead>
<tbody>
<tr>
<td>NSABP B-31</td>
<td>947</td>
<td>NR</td>
<td>3.8</td>
</tr>
<tr>
<td>NCCTG N9831</td>
<td>570</td>
<td>NR</td>
<td>3.3</td>
</tr>
<tr>
<td>BCIRG 006 *</td>
<td>1068</td>
<td>18</td>
<td>1.9</td>
</tr>
<tr>
<td>HERA</td>
<td>1678</td>
<td>3.0</td>
<td>0.6</td>
</tr>
</tbody>
</table>

modified from Telli M et al. JCO 2007(25):3525
BCIRG-006

- 7 LVEF measurements
- Symptomatic HF
  - AC-T 0.7%
  - AC-TH 2.0%
  - TCH 0.4%
- N=1068

What is the clinical significance of asymptomatic drops in LVEF?

Burden of cardiac testing

- 25,000 new cases of BC in Canada/yr
- 15% HER-2 positive (3750 patients)
- 3,000 pts (80%) receive adjuvant trastuzumab
- 3,000 x 6 echos/MUGA's = 18,000 tests/year
- US: 180,000 tests/year

Are we improving cardiac safety?
• The association between asymptomatic LVEF decline and CHF is unclear
• There is a risk patients will be wrongly identified as having cardiotoxicity which may compromise delivery of curative therapy
• The available evidence does not definitively support a specific schedule of screening nor does it demonstrate improved outcomes for screened patients
Cardiotoxicity Detection with Trastuzumab

Pre-Chemo:
Risk Score
Echo GLS / EF

Post-Chemo
Echo:GLS/EF
TnI

High Risk:
risk score ≥ 4 or
GLS < 16 or
EF < 53%

Low Risk:
risk score < 4 and
Baseline GLS ≥ 16 and
GLS ↓ < 3 units and
EF > 53% and
TnI normal

Cardiology Referral
Q3 monthly monitoring

Less Frequent Cardiac Monitoring

High Risk:
risk score ≥ 4 or
GLS < 16 or
GLS ↓ ≥ 3 units from baseline or
GLS < 16 or
EF < 53% or
TnI abnormal

Cardiology Referral
Q 3 monthly monitoring

Trastuzumab q3 wks X 54 wks

Risk Score¹:
Anthracycline = 2
Age 75-79 = 1
Age 80+ = 2
CAD = 2
AFib/Flutter = 2
Diabetes = 1
HTN = 1
Renal Failure = 2

The Ottawa Cardio-Oncology Model

How can we improve cardiac safety/reporting in cancer clinical trials?
Oncology Drug Development
How can we improve cardiac safety monitoring in cancer clinical trials?

- Include clinicians in initial stages of clinical trial design (phase I-III)
- Use common terminology (definitions) across trials (e.g., trastuzumab)
- Prospective collection of “core” cardiovascular data in all cancer therapeutic trials
### Baseline Cardiac Risk Factor and Diagnosis Assessment

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>Diagnosis</th>
<th>Diagnosis Date</th>
<th>Diagnosis</th>
<th>Diagnosis Date</th>
<th>Diagnosis</th>
<th>Diagnosis Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aortic Aneurysm (Thoracic or Abdominal)</td>
<td></td>
<td>□</td>
<td>□ Ethanol use (Heavy, as defined by &gt; 2 drinks/day and daily)</td>
<td></td>
<td>□ Pericarditis</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
<td></td>
<td>□</td>
<td>□ Endocarditis</td>
<td></td>
<td>□ Prior chest radiotherapy</td>
</tr>
<tr>
<td></td>
<td>Atrial flutter</td>
<td></td>
<td>□</td>
<td>□ Family history of</td>
<td></td>
<td>□ Prior chemotherapy</td>
</tr>
</tbody>
</table>

### Followup Cardiac Medications

- Aspirin
- Ace-inhibitor
  - *(e.g., Altace/Ramipril, Capoten/captopril, Lotensin/beazapril, Prinivil/Zestril/Listopril, Captopril/enalapril)*
- Angiotensin Receptor Blocker
  - *(e.g., Atacand/candesartan, Avapro/irbesartan, Cozaar/losartan, Divan/valsartan, Benicar/Olmesartan)*
- Beta-Blocker
  - *(e.g., Betapace/Sotalol, Coreg/Carvedilol, Tenormin/atenolol, Toprol/Metoprolol)*
- Alpha blocker
  - *(e.g., Minipress/prazosin, Hycrin/terazosin, Catapres/clonidine, Flomax/tamsulosin, Cardura/doxazosin)*
How can we improve cardiac safety monitoring in cancer clinical trials?

• Consult clinicians throughout the trial at specified time points to detect “early” signals of cardiotoxicity (“real time”)

• Consistent cardiovascular imaging techniques (eg. ECHO) or testing for a class of drug
How can we improve cardiac safety monitoring in cancer clinical trials?

• Post-marketing: collection of safety data to determine impact of new cancer drugs in the non-clinical trial setting (registry data)
• Rapid sharing of cardiac safety signals with clinicians and regulatory authorities
What are the benefits to clinicians?

CDK 4/6 inhibitor trial

Increased risk of ventricular tachycardia

External review: QTc=560 ms: QTcF = 648 ms

$$QTcF = \frac{QT}{\text{CubeRoot} RR \text{(seconds)}}$$
Cardiac Safety Monitoring in “real” time

Baseline risk
Core CRF
Define CV endpoints

Cardiovascular surveillance

Adverse event

Modification of protocol

Successful completion of study

cardiaconcology.ca
Thank-you!