FDA Perspective: How Does Cardiotoxicity Impact Drug Approval?

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Outline

• Background: Cancer Therapy Evolution
• Cardiovascular Adverse Events
• Benefit: Risk Considerations
• What do we do today
• What is missing or needs improvement
Cancer Therapy Evolution

Past
Drugs

Which patients respond best?

Current and future
Determine molecular profile of the patient’s tumour

Determine which drugs are most appropriate

Yap, Nat Rev Cancer, 2010
## Cardiovascular Adverse Effects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cardiomyopathy</th>
<th>Ischemia</th>
<th>↑ Arrhythmias QT prolongation</th>
<th>↑ BP</th>
<th>Pericardial Disease</th>
<th>PE DVT ATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti HER 2</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>TKIs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>VEGF Inhibitors</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Radiotherapy</td>
<td></td>
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<td></td>
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<td></td>
<td>X</td>
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<tr>
<td>Tamoxifen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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</tbody>
</table>
Consider Benefit of Cancer Treatment and Risk of Cardiotoxicity

- During drug development
- When evaluating the drug for regulatory approval
- When the clinician considers treating the patient
Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) updated (2005-6) meta-analyses

Breast Cancer Mortality

Death rates (% / year: total – rate in women without recurrence) & logrank analyses

Peto et al, SABCS 2007
Anthracycline Cumulative Dose and CHF Risk

Trastuzumab Survival: Metastatic Breast Cancer

- Chemotherapy (AC or Paclitaxel)
- Herceptin
- Chemotherapy Alone

Graph showing survival probability over months with risk ratio and 95% CI.
## Incidence of Cardiac Dysfunction in Trastuzumab MBC studies

<table>
<thead>
<tr>
<th>Arm</th>
<th>NYHA I-IV Trastuzumab</th>
<th>NYHA I-IV Control</th>
<th>NYHA III-IV Trastuzumab</th>
<th>NYHA III-IV Control</th>
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</thead>
<tbody>
<tr>
<td>AC</td>
<td>28%</td>
<td>7%</td>
<td>19%</td>
<td>3%</td>
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<tr>
<td>Paclitaxel</td>
<td>11%</td>
<td>1%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Mono therapy</td>
<td>7%</td>
<td>N/A</td>
<td>5%</td>
<td>N/A</td>
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</table>
# Trastuzumab Adjuvant Trials

<table>
<thead>
<tr>
<th>Studies</th>
<th>DFS</th>
<th>CHF Incidence</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>$p$ Value</td>
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<tr>
<td><strong>NSABP B31/NCCTG 9831</strong></td>
<td>0.48</td>
<td>&lt; 0.0001</td>
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<tr>
<td>AC → TH vs AC → T</td>
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<tr>
<td><strong>HERA</strong></td>
<td>0.54</td>
<td>&lt; 0.0001</td>
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<td>Chemo → H vs obs</td>
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<tr>
<td><strong>BCIRG 006</strong></td>
<td>0.67</td>
<td>&lt; 0.0006</td>
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<td>TCH vs AC → T</td>
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<tr>
<td>AC → TH vs AC → T</td>
<td>0.60</td>
<td>&lt; 0.0001</td>
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</table>
Where are we now?

- Breast cancer mortality is decreasing
- Therapy based on molecular subtypes
- Identifying patients who don’t need anthracyclines
- Combination therapies increase risk of cardiotoxicity
- Need to decrease cardiotoxicity
When to do Cardiovascular Monitoring During Drug Development

1. Drug Class
   - If drugs with similar targets have known cardiovascular toxicity
   - If there is tissue cross-reactivity (biologics)
   - If MOA/pathway/knockouts suggest cardiovascular toxicity

2. Pre-Clinical Studies
   - ECG changes in non-rodents
   - Histopathology (myocardial necrosis, significant inflammation)

3. Clinical
   - Cardiotoxicity in another clinical study
   - Combination therapy with overlapping cardiotoxicity
   - Patient population at increased risk e.g. prior anthracycline therapy, prior chest radiotherapy, ischemia
Recommendations for Phase 1 and 2 Studies

- Specific eligibility criteria: exclude patients at risk
- Conservative dose-escalations due to cardiac concerns
- Baseline and follow-up monitoring including ECG, LVEF (Echo or MUGA), frequent BP and QTc assessments
- Criteria for dose modifications, delays and drug discontinuations
- Criteria for rechallenge
- QT prolongation studies
Recommendations for Phase 3 Studies

- Definition of cardiac events
- Stopping rules for excess cardiac toxicity
- Use same cardiac imaging modality throughout the study
- Central reading recommended to avoid reader variability
- Endpoints: cardiac safety may be needed as a co-primary endpoint
- Long term follow-up
What is Missing or Does Not Work Well Today

- Better understanding of cardiotoxicity and repair at clinical and molecular level
- Identify patients at risk of cardiotoxicity
- Decrease cardiotoxicity risk:
  - early serum cardiac biomarkers
  - chemoprotection
- Early detection of cardiotoxicity
- Need good evidence addressing optimal monitoring intervals