Safety Pharmacology Strategies to Support Drug Development: Oncology Biotherapeutics

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Outline

- Biotherapeutics & Oncology Drug Development
  - Large Molecules
  - Vaccines

- ICH S9: Paradigm Change
  - Safety Pharmacology Integration into Toxicology Studies
Safety Pharmacology (SP) Assessment of Biopharmaceuticals: A Survey of Past Practice

All Biological License Approval (BLA) approvals (1980-2011) were reviewed (FDA & Pharmapendium sites)

<table>
<thead>
<tr>
<th>Modality</th>
<th>BLA#</th>
<th>Dedicated SP</th>
<th>Integrated SP</th>
<th>No SP</th>
<th>No Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibodies</td>
<td>33</td>
<td>10</td>
<td>6</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Proteins &amp; Peptides</td>
<td>25</td>
<td>9</td>
<td>3</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Enzymes</td>
<td>17</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Cytokines</td>
<td>15</td>
<td>3</td>
<td>0</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>91</td>
<td><strong>24</strong></td>
<td><strong>11</strong></td>
<td><strong>30</strong></td>
<td><strong>26</strong></td>
</tr>
<tr>
<td>% of Total</td>
<td>-</td>
<td>26</td>
<td>12</td>
<td>33</td>
<td>29</td>
</tr>
</tbody>
</table>

Integrated SP: SP endpoints were evaluated in toxicity studies
No SP: no SP studies were performed (stated)
No Data: No pharmacology/toxicology reviews found

HM Vargas et al., Expert Opinion Drug Safety 2012 (in review)
Biological License Approvals (1980-2011): Oncology vs Non-Oncology

- Oncology: 23
  - mAb: 16
  - Proteins: 1
  - Enzymes: 3
  - Cytokines: 3

- Non-Oncology: 68
## Cardiovascular Side-effects of Cancer Drugs

<table>
<thead>
<tr>
<th>CV issue</th>
<th>Anti-cancer Drug Type</th>
<th>Reversible</th>
<th>Irreversible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>Anthracyclines (doxo)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>HER2/ErbB2 inhibitors (lapatinib)</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Cardiac dysfunction &amp; Heart failure</td>
<td>Anthracyclines</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>HER2/ErbB2 inhibitors (trastuzumab)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Anti-VEGF</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>Anti-VEGF</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Ischemia; thrombo-embolism</td>
<td>Antimetabolites (5FU; capecitabine)</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>Anti-VEGF (bevaziciumab, sunitinib, etc.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+++: frequent  
++: common  
+: rare

Modified from: S Stortecky and TM Suter (2010)
Cardiac Contractility & Dysfunction
A Real Safety Concern for Oncology Drugs

- Several anti-cancer drugs cause contractile dysfunction*:
  - Oncology SM: Doxorubicin, epirubicin, mitoxantrone, cyclophosphamide, 5-FU, capecitabine, sunitinib
  - Oncology LM: Trastuzumab

- Oncology agents may cause cardiac dysfunction because therapeutic targets/pathways also have a role in heart function
  - >30 kinases known to alter myocardial mechanics/function**

- Oncology patients may be susceptible to drug-induced cardiac dysfunction due to: age, co-morbidities, concomitant meds, prior chemotherapy

*: Slordal and Spigset, 2006
## General Non-clinical Study Requirements

<table>
<thead>
<tr>
<th></th>
<th>ICH S9 (SM &amp; LM) 2009</th>
<th>ICH S6R1 (LM) 2009</th>
<th>ICH M3R2 (SM) 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Repeat-dose studies</strong></td>
<td>1 mo, supports P1 and P2</td>
<td>≤1 mo, supports P1</td>
<td>≤1 mo, supports P1</td>
</tr>
<tr>
<td><strong>Repeat-dose chronic studies</strong></td>
<td>3 mo, supports P3/filing</td>
<td>6 mo (1 sp) as needed for clinical dosing duration, supports filing</td>
<td>6 mo (rodent) and 9 mo (non-rodent) as needed for clinical dosing duration, supports filing</td>
</tr>
<tr>
<td><strong>Safety Pharm</strong></td>
<td>No dedicated studies; Integrate into toxicity studies (unless warranted)</td>
<td>No dedicated studies; Integrate into toxicity studies (unless warranted)</td>
<td>Dedicated studies (ICH S7A/B)</td>
</tr>
<tr>
<td><strong>Genotoxicity</strong></td>
<td>For marketing</td>
<td>Not warranted</td>
<td>Supports P1</td>
</tr>
<tr>
<td><strong>Repro Tox</strong></td>
<td>Embryo-fetal, supports marketing</td>
<td>Embryo-fetal, supports P3; Peri-postnatal, supports marketing</td>
<td>Fertility and embryo-fetal, supports P3; Peri-postnatal, supports marketing</td>
</tr>
<tr>
<td><strong>Carcinogenicity</strong></td>
<td>Not warranted</td>
<td>Not generally warranted</td>
<td>2 species, supports marketing</td>
</tr>
<tr>
<td><strong>Misc</strong></td>
<td>Phototoxicity, Local tolerance, Impurities: assessment and justification with filing</td>
<td>Phototoxicity: not warranted Tolerance: not warranted Impurities: as indicated by data</td>
<td>Local tolerance: conduct Phototoxicity, Impurities: as indicated by data</td>
</tr>
</tbody>
</table>

*Note: Differences in regulatory requirements*
SP Approach Described in S9: Impact

- Move away from performance of “box-checking” SP studies
- Reduce animal use during non-clinical toxicology phase
- Maximize SP data collection in toxicology studies

Challenge:

How to optimize SP evaluation in toxicology studies?
Example: Oncology Biotherapeutic
28 day toxicity study (6 mon recovery)

- Large molecule linked to cytotoxic agent
  - Antibody-drug conjugate

- Doses selected to achieve multiples over expected clinical range
  - Toxicity anticipated at high dose

- Relevant Species: Cynomolgus monkey (m/f)

- Dose groups
  - Vehicle (n= 5/sex)
  - Low (n= 3/sex)
  - Mid (n=5/sex)
  - High (n=3/sex)

- Weekly dosing (long half-life)
## Schematic of Sample Timing

### Sample Collection Schedule with JET-ECG Integration

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Group(s)</th>
<th>Time Point (relative to dosing)</th>
<th>Samples Collected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prestudy I</td>
<td>1-4</td>
<td>NA</td>
<td>Hem, Chem, Coag</td>
</tr>
<tr>
<td>Prestudy II</td>
<td>1-4</td>
<td>NA</td>
<td>Ab, Hem, Chem, Coag</td>
</tr>
<tr>
<td>Pre- (Day -3)</td>
<td>1-4</td>
<td>NA</td>
<td>JET-ECG (baseline)*</td>
</tr>
<tr>
<td>Day 1</td>
<td>1-4</td>
<td>Post dose</td>
<td>TK: many sample collections</td>
</tr>
<tr>
<td>Day 3</td>
<td>1-4</td>
<td>51-78 hr</td>
<td>JET-ECG</td>
</tr>
<tr>
<td>Day 8 (dose2)</td>
<td>1-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 15 (dose3)</td>
<td>1-4</td>
<td>TK-pre dose</td>
<td></td>
</tr>
<tr>
<td>Day 22 (dose 4)</td>
<td>1-4</td>
<td>TK, Ab, Hem, Chem, Coag</td>
<td></td>
</tr>
<tr>
<td>Day 22</td>
<td>1-4</td>
<td>Post-dose</td>
<td>TK: many sample collections</td>
</tr>
<tr>
<td>Day 24</td>
<td>1-4</td>
<td>51-78 hr</td>
<td>JET-ECG</td>
</tr>
<tr>
<td>Day 26</td>
<td>1-4</td>
<td>96 hr</td>
<td>TK, Hem, Chem, Coag</td>
</tr>
<tr>
<td>Day 29</td>
<td>1-4</td>
<td>168 hr</td>
<td>TK</td>
</tr>
</tbody>
</table>

*: 2 jacket acclimations prior to baseline
SP Data Collection and Analysis Protocol

- **ECG/HR:** Data collected continuously and divided into 6 hour segments
  - Analysis time: day, night, following day (around Cmax)
  - Analysis sub-blocks: 3 hr segments
  - Day/night time blocks compared to predose time blocks (day -3)
  - Quantitative analysis: library of ECG waveforms collected per animal on each collection day
  - Qualitative analysis: 1 to 1.5 minute of data taken at 12 hour intervals
  - BP: not assessed
    - JET-BP not available
    - HDO/cuff not adequate

- **CNS/RESP:** qualitative assessment taken as part of clinical observations
The Parallel Dose Group Design: Large volume of ECG data to CRUNCH!

- **Standard Telemetry (LSCO):** 8 animal x 4 doses
  - 32 animal-data days; plus 8 baseline days
  - **Total:** 40 animal-data days

- **JET-ECG:** n=5, 3, 5, 3/sex (32 total)
  - Day -3: 32 animal-data days (baseline)
  - Day 3: 32 animal-data days
  - Day 23: 32 animal-data days
  - Recovery: (2 veh, 2 MD/sex): 8 more
  - **Total:** 104 animal-data days

- Prompt turnaround of data requires aggressive and efficient resourcing
## Study Design Impact on Statistical Power

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Group Size</th>
<th>Values</th>
<th>PR</th>
<th>QRS</th>
<th>QT</th>
<th>QTc</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4DCO</td>
<td>N=8</td>
<td>Baseline</td>
<td>79</td>
<td>34</td>
<td>258</td>
<td>336</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absolute Δ</td>
<td>2.1</td>
<td>0.5</td>
<td>12.3</td>
<td>10.8</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%Δ</td>
<td>2.3</td>
<td>1.6</td>
<td>5.3</td>
<td>3.9</td>
<td>8.4</td>
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<tr>
<td>2DCO</td>
<td>N=6</td>
<td>Baseline</td>
<td>85</td>
<td>35</td>
<td>242</td>
<td>343</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absolute Δ</td>
<td>2.9</td>
<td>3.4</td>
<td>5.6</td>
<td>2.5</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%Δ</td>
<td>2.3</td>
<td>9.7</td>
<td>2.3</td>
<td>0.7</td>
<td>6.7</td>
</tr>
<tr>
<td>Parallel</td>
<td>N=3</td>
<td>Baseline</td>
<td>78</td>
<td>31</td>
<td>265</td>
<td>347</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absolute Δ</td>
<td>29</td>
<td>16</td>
<td>157</td>
<td>111</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%Δ</td>
<td>37.2</td>
<td>52.1</td>
<td>59.3</td>
<td>31.9</td>
<td>63.7</td>
</tr>
<tr>
<td></td>
<td>N=5</td>
<td>Absolute Δ</td>
<td>19</td>
<td>11</td>
<td>104</td>
<td>74</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%Δ</td>
<td>24.6</td>
<td>34.3</td>
<td>39.1</td>
<td>21.3</td>
<td>41.9</td>
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<tr>
<td></td>
<td>N=10</td>
<td>Absolute Δ</td>
<td>13</td>
<td>9</td>
<td>71</td>
<td>56</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%Δ</td>
<td>17.0</td>
<td>27.9</td>
<td>26.9</td>
<td>16.0</td>
<td>27.8</td>
</tr>
</tbody>
</table>
Learnings: What Went Wrong

- Data collection
  - Unanticipated interruption
    - System overload? Minor impact.

- Unanticipated data loss due to test article toxicity
  - High dose animals euthanized prior to final data collection

- Increased QTc interval after repeated dosing
  - No effect after the first dose
  - Issue resolution: hERG Voltage clamp & trafficking assay
    - Conjugated cytotoxin: no direct or indirect effect on hERG channel
Learnings: What Went Right

- All 32 animals acclimated to jacketing well
  - Good circadian changes
  - No data loss due to jacket or battery failure

- Very good process for jacketing and verifying signal quality (high level technical skills)

- Good quality data over the study

- ECG analysis time integrated; no impact on overall toxicology study timeline

- No effect dose (NOEL) identified

- CV Risk Assessment enabled FIH start

- Data Submitted with IND; Accepted by FDA
Considerations for Next Study

- **Parallel design creates a statistical challenge**
  - Consider pooling data from males and females
  - Consider increasing number of animals in key groups

- **Treatment related toxicity: factor**
  - Toxicity was anticipated at high dose, so Mid-Dose had higher N

- **Issue resolution of unanticipated ECG effects**
  - Antibody-drug conjugate: CV risk presumed to be low based on target-specific delivery of warhead
  - Mechanism of QTc effect → no direct or indirect effects
    - secondary to temperature or morbidity?
  - QTc de-risking: hERG VC and trafficking assays took time
Vaccines: A Brief Comment

- **Oncolytic Virotherapy: a vaccine modality**
  - First in class: *Talimogene laherparepvec*

- **Non-clinical Safety Assessment:**
  - Regulatory Guidelines (WHO; ICHS6R1)

- **Safety Pharmacology:**
  - Case-by-case; Pragmatic
  - Incorporate into Toxicology (if possible)
    - Challenge: what if mouse is only relevant species? (T-VEC)

- **Regional Regulatory Need: Awareness**
  - Japan decision tree for SP (Sun et al., JPTM 65:49-57, 2012)
  - SP core package for cancer vaccine: example in literature
Summary

- **ICH S9: dedicated safety pharmacology (SP) studies are not required for oncology therapeutics**
  - SP challenge: coordination into repeat-dose toxicity studies
  - LM challenge: NHP are sole species

- **Biopharmaceuticals generally require case-by-case assessment:**
  - JET-ECG: can be used effectively to optimize cardiac intervals
  - CNS/RESP: qualitative acceptable

- **How to address other CV risks?: Gaps remain**
  - BP: Can jacket-based BP be used?
  - LV dysfunction: Can echocardiography be used, esp in NHP? (feasibility?; Sensitivity?)
Acknowledgements

Toxicology Sciences
- Rafael Ponce, PhD
- Michael Engwall, PhD

Biostatistics
- Jessie Gu, PhD