Preclinical Cardiovascular Safety in Oncology: Do We Need Plumbers, Electricians, or Strength Trainers?

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Plumbers, Electricians, Strength Trainers?

Lapatinib, imatinib, dasatinib, trastuzumab, cetuximab: no “cardiac AE” term common to all
Cardiovascular Safety in Oncology: Broad Range of Adverse Effects from Multiple Therapeutics

- Cytotoxic chemotherapy
- Hormone therapy
- Targeted (signaling) therapy
- Radiotherapy

Figure 1. Simplified spectrum of vascular disease/toxicity induced by chemotherapeutic agents.

Herrmann et al., Circ., 2016
Lack of Selectivity of Receptor Tyrosine Kinase Inhibitors Provides for Potential Multiple Toxicities

Figure 5  Kinase dendrogram interaction maps for imatinib, dasatinib and sunitinib. (a–c) Kinases that bind imatinib (a), dasatinib (b) and sunitinib (c) are shown in red circles; larger circles indicate higher-affinity binding. Interactions with $K_d<10$ are shown.

– Lydon  *Nature Med.*, 2009
Chronic Toxicities Pose Additional Challenges

Nonclinical models target different “durations”
- Acute Effects - Safety Pharmacology Studies
- Chronic Effects - Toxicology Studies

- Two effects often are not associated, links/causality of acute vs. chronic effects not easily addressed
  - Hypertension contributing to evolving pump impairment along with declining “contractility” reserve

- Identification of most prevalent acute CV toxicities could guide efforts on non-clinical studies, spur toxicity-focused research on mechanisms
  - Mitigate / Manage / Prevent
    - Differences in safety margins, risk/benefit ratios, may lessen interest in prevention

- Need for better predictive biomarkers
  - Utility of systems biology-based approaches
Hazard Identification as Primary Role of Preclinical Studies:

- Risk assessment influenced by uncertain efficacy, type of adverse effect, ability to monitor adverse effect(s), reversibility of effect(s)
Hemodynamic: Hypertension with VEGF Inhibitors

**Sunitinib**
- Small molecule multiple tyrosine kinase inhibitor that blocks downstream VEGF signaling.
- Dose-dependent increase in mean arterial pressure upon start of dosing, telemeterized rats
- Hypertension reversible with some (but not all) antihypertensives
- Dose-dependent risk of hypertension clinically

**Bevacizumab**
- Neutralizing VEGF mAb to inhibit EGFR2-mediated tumor angiogenesis; also acts to prevent activation of VEGF1,2 receptors on endothelial cells.
- Three repeat dose tox studies (26 wks), cynomolgus monkeys: small rise in blood pressure, female monkeys (anest.), 26 wks (50 mg/kg/wk, [BLA]).
- Dose-dependent risk of hypertension clinically (Totzeck, JAHA, 2017)
- Single administration of BVZ (cross-reacting with murine receptors) increased mean arterial pressure measured at 7 & 14 days post admin.
- Echo: progressive decrease LVEF and increase LVEDD days 12-14

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**Mean Arterial Pressure, Mice**

- Baseline
- Day 7
- Day 14

Saline (n=5)

BVZ (n=35)

adopted from Borker et al., 2016
Structural-Contractile-Heart Failure: Multiple Contributing Factors

<table>
<thead>
<tr>
<th>Cardiomyocyte (Intrinsic)</th>
<th>Paracrine</th>
<th>Cardiac Progenitor Cells</th>
</tr>
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<tbody>
<tr>
<td>Oxidative Stress</td>
<td>ErbB2</td>
<td>Anthracyclines</td>
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<td>DNA Damage</td>
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<td>Energetics</td>
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Preclinical assessment difficult for other than short-term ventricular dysfunction

- Same limitations shared with HF efficacy studies
  - Echo studies not typical, biomarkers not clearly delineated, Comorbidities/combo drugs unresolved

Present Best: short term telemetry studies (dP/dTmax) and longer term toxicologic studies (morphology) to indirectly assess structural-contractile-failure

Studies of reversibility informative and essential
Can Patient-Derived Stem Cell Cardiomyocytes Be Used to Predict Patient-Specific Adverse Effects?

Suggestion: predicting susceptibility to clinical doxorubicin-induced cardiotoxicity using patient-specific hiPSC-CM’s (skin fibroblasts) \textit{in vitro}

- Comparing Healthy vs. Dox vs. DoxTox patients (4 pts/group)
- Doxrazoxane found not cardioprotective; antioxidant NAC was beneficial
- Study not prospective, other studies ongoing
Conclusions

Oncologic therapeutics typically affect multiple off-target sites/functions (both cardiac and non-cardiac)
- Possible differences: small molecules vs. targeted biologics

Diverse “spectrum” of on- and off-target effects between (and within) different drug classes
- Impossible to “cover” all aspects, know all mechanisms
- Phenotypic screens useful for early hazard assessments
- Mechanistic studies useful when spectrum of off-target effects or unanticipated on-target effects better understood

Acute functional effects more easily detected, longer term effects may first appear in clinic (especially likely for biologics?)
- Subsequent nonclinical studies to “loop back”, search for followers with lesser off-target adverse effects
Conclusions

Hazard Identification as Primary Role of Preclinical Studies

- Early nonclinical studies best inform on acute risk with patients
- Clinical studies often bypass “normal” subjects
- Oncology drugs pose greater challenges defining risk/benefit ratios
- Risk assessment influenced by uncertain efficacy, type of adverse effect(s), ability to monitor adverse effect(s), reversibility of effect(s), cofounding comorbidities

Secondary role of preclinical models
- Assess mitigation of CV effects

Promising role of patient-specific stem cell derived cardiomyocytes as part of the future of personalized medicine
Thanks for your attention.

Sunrise, International Space Station. NASA.