Perspectives on Evaluating and Managing Cardiovascular Safety Risk for Anticancer Drugs

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“The views presented do not reflect an official position or policy of the National Cancer Institute or the U.S. Government.”
Goals

Review a Clinical Definition of Drug-Associated Cardiotoxicity and Relevance to Oncology

Discuss Approaches to Cardiotoxicity for Oncology Agents

- Determine Manageability
- Translate mechanistic understanding into opportunities
- Anticipate cardiac liabilities early and test hypotheses
Why Focus on the Heart?
A target organ that Anticancer Agents Should Avoid

• It is increasingly probable that a patient may have cancer and cardiovascular disease

• Combination therapy often amplifies cardiotoxicity; particularly when combined with chemotherapy

• Knowledge of the risk of toxicity can help clinicians choose the optimal and least toxic regimen suitable for the individual patient.

• Identification of mechanisms (i.e. cell signaling pathways) can be a basis for the management of drug-induced cardiotoxicity.
What is Drug-Associated Cardiotoxicity?

• A clinical definition of cardiotoxicity provided by the cardiac review and evaluation committee supervising trastuzumab clinical trials is:
  – Cardiomyopathy in terms of a reduction in left ventricular ejection fraction (LVEF)
  – Symptoms and signs associated with heart failure
  – S3 gallop, tachycardia, or both
  – Reduction in LVEF from baseline or a reduction in LVEF in the range of equal to or greater than 10% to less than 55%, without signs or symptoms

• Note: This definition did not include subclinical cardiovascular damage that may occur in response to chemotherapeutic agents
Managing Cardiac Toxicity
Romidepsin (FK228; NSC-630176; Depsipeptide)

- Isolated from *Chromobacterium violaceum*
- Induced morphological reversion of H-ras transformed NIH3T3 Cells
- Inhibits proliferation and induces apoptosis in tumor cell lines
- Interferes with mitogen-induced signaling pathways
- Activated in vivo by glutathione
- Shown to be an HDAC inhibitor (HDAC1 and HDAC2)
- **Dropped by Fujisawa** due to cardiotoxicity in the dog
- NCI applied a tailored approach to widen the margin of safety and move forward to the clinic
Initial Preclinical Profile for Cardiac Toxicity of Romidepsin in Dogs

- Administered up to 4.0 mg/kg/week for 4 weeks (given 1.0 and 2.0 mg/kg/day twice a week for 4 weeks) did not produce any mortality.
- Prolonged QT interval was noted at both doses and an increase in the ST segment occurred in dogs in the 2.0 mg/kg/day dose group.
- Myocardial hemorrhage, atrophy and/or necrosis and intestinal erosion was seen.
- Thickening of epicardium and pericardium and renal/pulmonary foci were observed.
### NCI: Response of Advanced Stage, Subcutaneous LOX IMVI Melanoma Xenografts to Romidepsin

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Route of Admin</th>
<th>Dose mg/kg</th>
<th>Maximum number of complete Regressions</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once Every 4&lt;sup&gt;th&lt;/sup&gt; day x 3</td>
<td>IV</td>
<td>5.3</td>
<td>10/10</td>
<td>0/10</td>
</tr>
<tr>
<td>Once per day x 5</td>
<td>IV</td>
<td>1.44</td>
<td>3/10</td>
<td>0/10</td>
</tr>
<tr>
<td>Once Every 4&lt;sup&gt;th&lt;/sup&gt; day x 3</td>
<td>IP</td>
<td>5.30</td>
<td>2/10</td>
<td>3/10</td>
</tr>
<tr>
<td>Once per day x 5</td>
<td>IP</td>
<td>1.44</td>
<td>0/10</td>
<td>0/10</td>
</tr>
<tr>
<td>Once every 3 hr x 8 doses (day 4 &amp; 8)</td>
<td>IP</td>
<td>0.66</td>
<td>0/10</td>
<td>10/10</td>
</tr>
</tbody>
</table>

Total Number of Schedules Tested = 8
3 dose levels each and two routes of administration
Romidepsin (FK228; NSC-630176)  
Schedule-Dependent Toxicity in the Dog

<table>
<thead>
<tr>
<th>Schedule/Route</th>
<th>Deaths</th>
<th>Cardiotoxicity?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose 2.0 mg/kg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 Hr iv – Once Every 4th day x 3</td>
<td>4/4</td>
<td>Yes</td>
</tr>
<tr>
<td>1 Hr iv – Twice per week x 4</td>
<td>1/2</td>
<td>Yes</td>
</tr>
</tbody>
</table>

| **Dose 1.0 mg/kg**                                  |        |                 |
| Bolus iv – Once                                     | 3/3    | Yes             |
| 4 Hr iv – Once Every 4th day x 3                    | 0/4    | No              |

Studies in dogs demonstrated that the length of time over which drug is administered markedly affects the toxicity of this drug.

- Bone marrow toxicity was considered dose limiting in rats and gastrointestinal and site of infusion toxicity was dose limiting in dogs.
Commercial Development of Rhomodepsin

- In 2004, Gloucester Pharmaceuticals, Inc. USA, licensed the exclusive rights for commercial development.
- QT interval prolongation and ST segment abnormalities observed in phase I studies.
- Intensive cardiac monitoring was incorporated into all clinical trials.
- The most frequent toxicities of romidepsin include nausea, vomiting, fatigue and myelosuppression.
- Electrocardiographic (ECG) changes were common, but are not associated with myocardial damage.
- On November 5, 2009, FK228 was approved by FDA for treating patients with CTCL.
Managing Cardiotoxicity

• Establish Schedule dependency; Discover a schedule to retain efficacy and mitigate toxicity
  • Intermittent Schedule Active and Less Toxic
  • *Cardiotoxicity may be observed in the specie used for efficacy, thus monitoring could be informative*

• Adequate Characterization of toxicity
• Determine if toxicity can be monitored
Mechanistic Understanding
Mice lacking the ABCB1-type P-glycoprotein have higher intracardiac concentrations of romidepsin that correspond to changes in QT prolongation.
ADME Relevant to Cardiac Toxicity

- Mice lacking the ABCB1-type P-glycoprotein have higher intracardiac concentrations of romidepsin that correspond to changes in QT prolongation.
- **Patients carrying genetic variants** that could raise ABCB1 expression in the cardiac endothelium have lower ΔQTc following a single dose of romidepsin.
- Certain **commonly inherited polymorphisms in ABCB1** may serve as markers for QT prolongation following the administration of ABCB1-substrate drugs.
Cardiotoxicity Assessments in vitro

- Toxicity of romidepsin (0.1-100 μM) to cardiac myocyte cultures derived from rat, dog and an immortalized cardiac myocyte cell line W1 was determined.
- Cell cultures were assayed for viability using the MTT dye exclusion assay and for extracellular LDH levels.
- Romidepsin caused a concentration dependent release of LDH in all 3 myocyte models (rat, dog and human).
- Romidepsin exhibited greater cytotoxicity in myocytes derived from all three species than minoxidil or doxorubicin.
**In vitro** Measures of Cell Viability and Arrhythmias: Cultured human Cardiac Myocytes

**A** Cell Viability - ATP Levels

**B** Apoptosis

**C** Mitochondrial Function

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**Action Potential Prolongation by Ion Channel Blockers**

**Terfenadine**

- **EC<sub>50</sub> = 21 μM**

**Terfenadine**

- **Negative Control**

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**% Change in Action Potential**

- Terfenadine
- Negative Control

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**% Change in Action Potential**

- Terfenadine
- Negative Control

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**% change of APD<sub>90</sub> (ms)**

- Terfenadine

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**EC<sub>50</sub> = 1 nM**

Lot 1

Lot 2
Comparative Cardiac Myocyte Toxicity of NSC613009 (Jaspamide) & NSC630176 (Romidepsin)

Shown: An in vitro cardiac toxicology study using human induced pluripotent stem cell (hiPSC)-derived cardiomyocyte (CMs) and non-invasive impedance measurement with the xCELLigence RTCA Cardio-96

Readouts: Function (Beat Amplitude, Rate and Rhythm)

Conclusion: NSC613009 represents a typical cardiac myocyte toxicant and NSC630176 has complex effects on the cardiac function (and viability).

Unpublished work
Human hiPSC cardiomyocyte viability after Exposure to Jaspamide

Unpublished work
Beating Waveforms of hiPSC-derived Cardiomyocytes Exposed to Jaspamide

<table>
<thead>
<tr>
<th>(µM)</th>
<th>Pre-drug</th>
<th>0.5 hr</th>
<th>3 hr</th>
<th>12 hr</th>
<th>24 hr</th>
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<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
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<tr>
<td>10</td>
<td></td>
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<td></td>
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<tr>
<td>30</td>
<td></td>
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</tbody>
</table>

Unpublished work
<table>
<thead>
<tr>
<th>Channel</th>
<th>Mean % inhibition by Jaspamide</th>
<th>S.D.</th>
<th>S.E.</th>
<th>Positive Controlb</th>
<th>Mean % inhibition</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cav1.2</td>
<td>64.3</td>
<td>5.8</td>
<td>4.1</td>
<td>Nifedipine (1 µM)</td>
<td>87.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Cav3.2</td>
<td>48.8</td>
<td>0.5</td>
<td>0.4</td>
<td>Nickel (100 µM)</td>
<td>88.3</td>
<td>0.2</td>
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<tr>
<td>HCN2</td>
<td>41.3</td>
<td>0.6</td>
<td>0.4</td>
<td>Zatebradine(100 µM)</td>
<td>81.2</td>
<td>1.5</td>
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<tr>
<td>HCN4</td>
<td>7.3</td>
<td>1.1</td>
<td>0.8</td>
<td>Zatebradine(100 µM)</td>
<td>86.5</td>
<td>3.6</td>
</tr>
<tr>
<td>hERG</td>
<td>4.2</td>
<td>7.3</td>
<td>5.2</td>
<td>E-4031 (0.5 µM)</td>
<td>98.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Kir2.1</td>
<td>1.5</td>
<td>0.6</td>
<td>0.5</td>
<td>Barium (100 µM)</td>
<td>88.8</td>
<td>7.1</td>
</tr>
<tr>
<td>Kir3.1/3.4</td>
<td>-1.1</td>
<td>4.3</td>
<td>3.0</td>
<td>Barium (300 µM)</td>
<td>75.9</td>
<td>8.3</td>
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<tr>
<td>Kir6.2/SUR2A</td>
<td>-3.8</td>
<td>3.1</td>
<td>2.2</td>
<td>Glybenclamide (1 µM)</td>
<td>98.3</td>
<td>0.5</td>
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<tr>
<td>Kv1.5</td>
<td>98.5</td>
<td>0.1</td>
<td>0.0</td>
<td>4-AP (2000 µM)</td>
<td>87.0</td>
<td>0.2</td>
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<tr>
<td>Kv4.3</td>
<td>3.9</td>
<td>3.6</td>
<td>2.5</td>
<td>Flecainide (100 µM)</td>
<td>73.9</td>
<td>2.0</td>
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<tr>
<td>KvLQT/mink</td>
<td>14.8</td>
<td>1.2</td>
<td>0.9</td>
<td>Chromanol 293B (30 µM)</td>
<td>94.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Nav1.5 tonic</td>
<td>8.7</td>
<td>3.5</td>
<td>2.5</td>
<td>Lidocaine (2000 µM)</td>
<td>68.0</td>
<td>6.7</td>
</tr>
<tr>
<td>Nav1.5 phasic</td>
<td>18.8</td>
<td>0.4</td>
<td>0.3</td>
<td>Lidocaine (2000 µM)</td>
<td>68.0</td>
<td>6.7</td>
</tr>
</tbody>
</table>
Human hiPSC cardiomyocyte viability after Exposure to Jaspamide

Unpublished work
Incorporate ECG Monitoring into Efficacy Studies
What Are the Possibilities?

- A novel application of echocardiographic strain imaging was applied to mouse models of cardiovascular disease.
  - Strain is defined as the fractional or percentage change in an object's dimension in comparison to the object’s original dimension.
  - Speckle Tracking Echocardiography is a unique echocardiographic imaging technique that analyzes motion within an ultrasonic window by tracking interference patterns and natural acoustic reflections.

- In a mouse model of myocardial infarction (MI), echocardiographic strain-based measures allowed for assessment of global (whole heart) and regional (specific heart areas) cardiac function.
Speckle-tracking-based Strain Analysis

Normal ventricular function = myocardial deformation along the longitudinal, radial, & circumferential axes

acoustic back scatter on echocardiographic images

Curves (representing strain measures over time) generated for each of the six standard myocardial regions
Speckle-Tracking Echocardiography

Longitudinal strain

Radial strain

Circumferential strain
Biomarkers for Cardiac Injury in Rodent Studies
Target inhibition and cTnl concentration in serum from kinase inhibitor studies.

Engle S K et al. Toxicol Pathol 2009;37:617-628
Comparison of cardiac necrosis detected by histopathology and cTnI concentrations in serum.

Engle S K et al. Toxicol Pathol 2009;37:617-628
Screening Opportunities

Clinical-like Pre-clinical Safety Studies

• Investigate potential cardiac liabilities earlier
  ✓ mechanistic hypothesis can be addressed
  ✓ synthetic chemistry efforts can be used to screen out safety liabilities
• Predict most dose-limiting target organ toxicities observed in 4-week rodent studies using a short-term (4-7 day) repeat-dose study
• Perform initial biomarker exploration studies (or qualification), explore ways to monitor toxicity and perform pharmacokinetic evaluations.
Drug Development Partnerships with NCI

The NCI Experimental Therapeutics Program (NExT) - A prioritized pipeline of NCI-driven targeted therapeutics for development
http://dctd.cancer.gov/About/major_initiatives_NExt.htm

The NCI Chemical Biology Consortium (CBC) - a network of chemical biologists and molecular oncologists from industry and academia that aids the discovery of new agents to treat cancer

Cancer Therapy Evaluation Program (CTEP) coordinates clinical trials, as well as sponsoring other clinical research; works extensively with the pharmaceutical and biotechnology industries
http://ctep.info.nih.gov/

Developmental Therapeutics Program (DTP) coordinates preclinical evaluations and early in vitro screening
http://dctd.cancer.gov/ProgramPages/dtp/default.htm
Optional Material
removed before presentation