Cardiac Toxicity, Risk Management, and Oncology Drug Development

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Nov 4, 2011

Is cardiovascular toxicity with cancer therapy a reason to stop development of an effective cancer drug?

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Diverse Mechanisms for Cardiac Safety Issues in Oncology Drug Development

<table>
<thead>
<tr>
<th>QTC Prolongation</th>
<th>Coronary Syndromes</th>
<th>CHF</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic trioxide</td>
<td>5FU; Capcitabine</td>
<td>Doxorubicin</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Depsipeptide</td>
<td>Bevacizumab</td>
<td>Trastuzumab</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>VDAs</td>
<td>Sorafenib</td>
<td>Lapatinib</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VDAs (CA4P, ZD6128, MN-029)</td>
<td>Alemtuzumab</td>
<td>Sunitinib Axitinib</td>
</tr>
<tr>
<td>Geldanamycin analogues (17AAG, 17DMAG)</td>
<td></td>
<td></td>
<td>VDAs</td>
</tr>
</tbody>
</table>

Drug Information Association
www.diahome.org
Cardiovascular Safety Issues in Oncology Drug Development

Major Categories

• Vascular; Hyper/Hypotension, Vasospasm; thrombotic effects
• Cardiomyocyte damage
• Conduction abnormalities; Arrhythmias
• Renal or Metabolic effects

1. Is toxicity a reason to stop development?

2. Can successful Risk Management strategies be developed and employed?

3. Will the patient be toxicity-free if instead treated with current Standard of Care?
Risk Management of Hypertension in the Development of Axitinib

**Bedside rules for monitoring & management**

- Home BP testing
- For systolic BP >150 mm Hg or diastolic BP >100 mm Hg:
  - NO dose reduction or termination from protocol treatment
- New or additional antihypertensive treatment was initiated.
  - For patients on maximum antihypertensive treatment with continued hypertension, the axitinib or placebo dose was reduced one level.
- For systolic BP >160 mm Hg or diastolic BP >105 mm Hg, antihypertensive treatment was adjusted if appropriate
  - Axitinib or placebo dosing was interrupted and resumed at one lower dose level once the BP was < 150/100 mm Hg
- **Given successful management, starting dose of 5 mg escalated to 10 mg in patients who tolerate**


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**Axitinib Phase 3 Study in RCC**

**Frequencies of Hypertension and Discontinuation due to Adverse Event**

**Phase III Design:**
Patients with renal cell cancer randomized to Axitinib or Sorafenib
36.8 % of patients on Axitinib able to escalate dose

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Gr-3-4 BP</th>
<th>Discontinue due to AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>11%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Axitinib</td>
<td>15%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

Rini B et al, ASCO, 2011
**Axitinib Phase 3 Study in RCC**

*Frequencies of Hypertension and Discontinuation due to Adverse Event*

**Phase III Design:**
Patients with renal cell cancer randomized to Axitinib or Sorafenib
36.8% of patients on Axitinib able to escalate dose

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response Rate</th>
<th>Progression - Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>9.4%</td>
<td>4.7 months</td>
</tr>
<tr>
<td>Axitinib</td>
<td>19.9%</td>
<td>6.7 months*</td>
</tr>
</tbody>
</table>

*Hazard Ratio 0.665; p < 0.0001
Rini B et al, ASCO, 2011

**Axitinib Phase 3 Study in Pancreatic CA**

*Frequencies of Hypertension with SOC*

**Phase III Design: Randomized, Double Blind**
632 patients with pancreatic cancer randomized to standard Gemcitabine + Placebo or Gemcitabine + Axitinib

<table>
<thead>
<tr>
<th>Regimen</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem + Placebo</td>
<td>22 (7%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Gem + Axitinib</td>
<td>65 (21%)</td>
<td>20 (7%)</td>
</tr>
</tbody>
</table>

Vascular toxicity associated with common anticancer SOC  

5 Fluoro-uracil  

Mosseri, Fingert et al  Ca Res 53: 3028-3033, 1993

Axitinib-associated hypertension and clinical outcomes

Rixe O et al, ASCO, 2011 Abstract 5045
Bevacizumab-induced hypertension and clinical outcomes in Colon Cancer

![Graph showing survival probability](image)

With bevacizumab-related arterial hypertension

Without bevacizumab-related arterial hypertension

(P = 0.04)


Axitinib hypertension & clinical outcomes
Lack of relationship to AUC

![Graph showing overall survival](image)

Rixe O et al, ASCO, 2011 Abstract 5045
**QTc – Growing Impact on Oncology**

<table>
<thead>
<tr>
<th>Oncology Drug</th>
<th>Impact on Development &amp; Marketing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romidepsin® (Depsipeptide)</td>
<td>&gt;&gt;$100K vendor costs &amp; major logistic burden for the National Cancer Institute</td>
</tr>
<tr>
<td>ZD6474 (AZ)</td>
<td>QTc determines DLT</td>
</tr>
<tr>
<td>SR271425 (Sanofi)</td>
<td>QTc determines DLT</td>
</tr>
<tr>
<td></td>
<td>Development Terminated</td>
</tr>
<tr>
<td>Sprycel™ (dasatinib)</td>
<td>Product Label w ECG monitoring and special precautions</td>
</tr>
<tr>
<td>Zolinza® (vorinostat)</td>
<td>Product Label w ECG monitoring and special precautions</td>
</tr>
<tr>
<td>Tasigna® (nilotinib)</td>
<td>Product Label w Boxed Warning for QTc prolongation &amp; sudden death</td>
</tr>
</tbody>
</table>

**Cardiovascular Safety Issues in Oncology Drug Development**

**Major Categories**

- Conduction abnormalities;
- Arrhythmias

1. *Is toxicity a reason to stop development?*

2. *Can successful Risk Management strategies be developed and employed?*

3. *Will the patient be toxicity-free if instead treated with current Standard of Care?*
ZD6474 - adding QTc as Phase 1 Substudy

avoiding unintended consequences

• Phase 1 adds multiple ECGs without qualified protocol language to manage ‘unintended consequences’ from these results

• QTc prolongation in 4 patients dosed up to 300 mg
  → dose reduced 50% in 2 pts who then tolerate w/out QTc toxicity
  – These same pts then discontinue protocol due to PD

• Exposures predicted sub-therapeutic after same dose reduction
  – Doses ≥ 300 mg provide most reliable therapeutic exposures

• Nausea, anti-emetics in 15 patients (20%) on study
  – No analysis to correlate QTc with nausea
  – No consideration of QTc effects from antiemetics, other con meds

Reference: Holden SN et al, Annals of Oncology, May 19, 2005

Impact of Con Meds on QTc
and spurious findings for experimental anticancer agents

Example:
Ondansetron now
> off-patent
> wider uses likely

Zensana™ (Ondansetron)
Oral Spray – NDA planned

June 23, 2008 H.Fingert
Ondansetron PK Profile of 8 mg Zensana (Oral Spray) vs. Tablet

Oncologists use higher doses of conventional ondansetron (e.g. 16-32 mg) in clinical practice

Cardiac Safety Study
Early Development Protocol

- Goal to characterize QTc after high exposures expected post-approval.
- Similar to TQT: moxifloxacin; quality ECG & PK conditions, all subjects receive all treatments similar to a crossover
- Different from TQT: Broader eligibility; 1-day placebo; uniform granisetron; re-dosing & extended treatment; analysis employs mean change and categorical outliers
- Opportunities for research about QTc effects of uniform granisetron dose & schedule to prevent nausea
Roadmaps to Rational Combination Therapies for Breast Cancer


Managing CV and Metabolic Risks in Oncology Clinical Development

- MTOR- and PI3K-targeted agents developed by Dr. Josep Tabernero and colleagues at Vall d’Hebron Hospital, Barcelona & other Hospitals
- Hyperglycemia and -cholesterolemia recognized metabolic toxicities
- Risk management strategies successfully evaluated in early development programs

Novel Combinations and Improved Clinical Outcomes

- MTOR inhibitors show modest single agent activity in women with progressive breast cancer after 1st line hormone treatment.

- Phase 3 ‘BOLERO-2’ Study of Everolimus+Exemestane vs Placebo+Exemestane

- Planned to require 724 pts; stopped early by DSMB

- Significant efficacy advantage at first interim analysis: **Median PFS 11 v 4 months**

“…clinical development … will require a change from the current large, randomized trials in unselected patient populations to smaller trials in groups with a molecularly defined tumor type. Combinatorial approaches that act on the secondary mutations and/or compensatory pathways in resistant tumors may markedly improve on the effects of targeted agents used alone. Ref: Higgins and Baselga, J Clin Invest. 2011 Oct 3;121(10):3797-803.

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**CV risk management within Oncology Drug Development**


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“Continue anticancer therapy”
Lessons Emerging about CV Events in Oncology Drug Development

Associations with:
• Control agents used as Standard of Care (SOC)
• Agents targeting new MOA
• Concomitant medications

Why perform cardiac safety–directed research with products designed to treat advanced malignancy?

• Expanded uses of oncology products
  – Different risk-benefit for early or adjuvant settings
• Growing combinations, Novel-Novel regimens
  – Which agent should be adjusted if CV events are identified?
• Poly-pharmacy, incl. generic 5HT3 antiemetics, metformin for hyperglycemia

• It’s not simply about NDA approval
• Value of close collaboration with cardiovascular specialists
• Must understand & mitigate risk appropriately
  …and avoid unintended consequences
• Scientific investigations and validation of safety biomarkers remain an important question in clinical research & practice
Lessons

• More frequent & sensitive monitoring for CV events requires thoughtful protocol designs
  – Engagement of cardiologists/adjudication
  – Avoid unintended consequences
  – Preserve access to treatment & proper dosing
• Be prepared for CV events even with SOC
• Expanding development of novel combinations predicted to further increase possible CV risks
• Safety Risk Management is an alternative to…
  – Premature termination of development programs
  – Premature dose reduction/discontinuation for individual patients

Conclusions

• Cardiovascular liability is not a “no go” for oncology development, patient benefit, and regulatory approval
• Advantages to start in early development
• Expanding novel combinations will likely present more challenges about CV safety and risk management
• Need to recognize and avoid unintended consequences
  – including adverse impact on treatment access, dose modification, development timelines, burden to clinical sites
  – Appropriate use of safety markers, e.g. ECGs, troponin, BNP, MUGA, KIM-1, etc.
• Opportunities for research, innovation, dialogue:
  – Risk Management
  – New approaches to clinical/protocol development
  – Open dialogue with regulators, sponsors, clinicians, patient advocacy & professional organizations