Drug Development in Relapsed or Refractory Myeloma

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State of Affairs in Myeloma

- Myeloma remains incurable
- All patients eventually relapse requiring subsequent therapy
- Current therapeutic options are generally palliative
Targets of Relevance and Clinical Drug Development in Myeloma

• Proteasome is the most critical therapeutic target in myeloma independent of disease status

• Resistance to proteasome inhibition is a major clinical problem, and strategies to overcome an important clinical task

• Despite significant insight in Myeloma biology, clinical drug development in myeloma seems empiric!
Relapse vs. Resistant

• Is the biology of myeloma cells distinct in relapsed vs. relapsed and refractory?
  • chemotherapy resistant vs. novel therapeutics vs. combinations

• Does myeloma survival pathways converge at some point during resistant phase?

• Should these factors be considered in drug development?
## Bortezomib/DEX Combination

<table>
<thead>
<tr>
<th>Patients Type</th>
<th>Regimen</th>
<th>Phase</th>
<th>No. of Pts</th>
<th>Response ORR (CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rel¹</td>
<td>VD</td>
<td>II</td>
<td>15</td>
<td>74% (7%)</td>
</tr>
<tr>
<td>Rel/Ref²</td>
<td>VD</td>
<td>II</td>
<td>88</td>
<td>66.9%</td>
</tr>
<tr>
<td>Rel/Ref³</td>
<td>VD</td>
<td>II</td>
<td>70</td>
<td>59% (7%)</td>
</tr>
<tr>
<td>Rel⁴</td>
<td>V-CD</td>
<td>II</td>
<td>50</td>
<td>82% (16%)</td>
</tr>
<tr>
<td>Rel⁵</td>
<td>VMelD</td>
<td>I/II</td>
<td>53</td>
<td>68% (23%)</td>
</tr>
<tr>
<td>Rel/Ref⁶</td>
<td>VD-PDL</td>
<td>II</td>
<td>25</td>
<td>80%</td>
</tr>
<tr>
<td>Rel / Ref⁷</td>
<td>V-CD</td>
<td>II</td>
<td>67</td>
<td>88%</td>
</tr>
</tbody>
</table>

V; velcade, D; dexamethasone, C;cyclophosphamide, Mel; melphalan, PDL; pegylated liposomal doxorubicin.

1. Kropff et al 2005,(29);5 Leu Research
2. Kobayashi et al 2010 (92);4 Int Jour of Hemato
3. Corso et al 2009 (83);5 Eur Jour of Hema
4. Kropff et al 2007 (138);3 BJH
5. Popat et al 2009 (144);6 BJH
6. Gozzetti et al 2010 (10); 1 Clin Lym, Myel,& Leu
Bendamustine, bortezomib and dexamethasone (BVD) in elderly patients with relapsed/refractory multiple myeloma: The Intergroupe Francophone du Myélome (IFM) 2009-01 protocol

Philippe Rodon (1), Cyrille Hulin (2), Brigitte Pegourie (3), Mourad Tiab (4), Bruno Anglaret (5), Lotfi Benboubker (6), Henri Jardel (7), Olivier Decaux (8), Brigitte Kolb (9), Muriel Roussel (10), Laurent Garderet (11), Xavier Leleu (12), Olivier Fitoussi (13), Carine Chaleteix (14), Philippe Casassus (15), Pascal Lenain (16), Philippe Moreau (17), Marie-Odile Pétillon (12), Claire Mathiot (18), Hervé Avet-Loiseau (17)

Review

- ORR 57.5%
- IMiD failures had low response rate (52% vs. 83%)
- High risk patients also had lower ORR (Del17p⁺ = 20%, High B2M = 49%)
- 27% Stopped treatment
- 15% death rate for 2nd line treatment
My Assessment

• Significant toxicity in the elderly patients
• Responses no better than VD itself
• No significant improvement in depth of responses
• Triple drug combos with PDL or cyclophosphamide may perform better.
• In my practice I will be deterred from using this combo in 1st relapsed elderly.
PANORAMA 2: A phase II study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory multiple myeloma

## Bortezomib Refractory

<table>
<thead>
<tr>
<th>Patients Type</th>
<th>Regimen</th>
<th>Phase</th>
<th>No. of Pts (refractory)</th>
<th>Response (%)</th>
<th>ORR (CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rel/Ref(^1)* (\text{CREST})</td>
<td>VD</td>
<td>II</td>
<td>27</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Rel/Ref(^1)* (\text{SUMMIT})</td>
<td>VD</td>
<td>II</td>
<td>74</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Rel/Ref(^2)</td>
<td>VD</td>
<td>IIIB</td>
<td>141</td>
<td>11% (1%)</td>
<td></td>
</tr>
<tr>
<td>Rel / Ref(^3)</td>
<td>Perifosine + VD</td>
<td>I/II</td>
<td>84</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Rel/Ref(^4)</td>
<td>Vorinostat + V</td>
<td>I/II</td>
<td>9 (total 23)</td>
<td>33%</td>
<td></td>
</tr>
</tbody>
</table>

1. Jaggannath et al 2006 (91); 7 Hematologica
2. Mikhael et al 2009 (114); 2 BJH
3. Richardson et al JCO 2012
4. Badros et al 2009 (15) CCR
Review

• Design – Single arm, non-randomized
• Study Size - 55 patients
• Patients received multiple prior Bort regimens – median 2 (1-6)
• ORR = 31% (n=17)
• Average duration of exposure = 4.9 months
## Panobinostat (LBH589) in Myeloma (Overview)

<table>
<thead>
<tr>
<th>Patients Type</th>
<th>Regime</th>
<th>Phase</th>
<th>N</th>
<th>Prior Therapies</th>
<th>Response ORR/CR</th>
<th>Toxicity / Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rel / Ref¹</td>
<td>Pan</td>
<td>II</td>
<td>38</td>
<td>Median 5</td>
<td>2.6% (n=1)</td>
<td>34% G3/4 Hematologic</td>
</tr>
<tr>
<td>Rel / Ref²</td>
<td>MPT + Pan</td>
<td>II</td>
<td>31</td>
<td>2/3 had &lt;2 prior therapies</td>
<td>38.5% No CR</td>
<td>71% Neutropenia Rx Not well tolerated</td>
</tr>
<tr>
<td>Rel / Ref³</td>
<td>VD + Pan</td>
<td>III</td>
<td>672 (data on 267 only)</td>
<td>51% had 1 prior therapy</td>
<td>NA</td>
<td>Blinded data?</td>
</tr>
</tbody>
</table>

1. Wolf, JL Leu & Lym March 2012
2. Offidani et al Leu & Lym March 2012
3. San-Miguel et al ASH 2011
Considerations

• Addition of Dex can induce responses in Bort refract patients.

• How many patients had their last treatment as Bort/Dex or Bort?

• What was the median no. of treatments in the patient who demonstrate response?

• Median time from time of diagnosis?

• Average duration of response is not clear?
• Single agent does not work!
• Interesting combination Data
• Difficult patient population
• Patient heterogeneity precludes practice changing conclusions
• Exact role of Panobinostat in MM and the extent of its potential benefit remain to be addressed through larger randomized studies
Phase I Trial of Obatoclax Mesylate in Combination with Bortezomib for Treatment of Relapsed Multiple Myeloma

Alexander K. Stewart\textsuperscript{1}, Suzanne Trudel\textsuperscript{2}, Jeffrey A. Zonder\textsuperscript{3}, Suzanne Hayman\textsuperscript{1}, Charles Erlichman\textsuperscript{1}, Briant Fruth\textsuperscript{1}, Betsy LaPlant\textsuperscript{1}, Daniel Sullivan\textsuperscript{4}
Bcl-2 and Myeloma

- Another important target in MM
- Extensive preclinical data support targeting Bcl-2 in MM
- Obatoclax also demonstrated promising in vitro activity
- Clinically too toxic in the combination studied
- Is the target still clinically important?
• Do we really know which pathway is critical at which stage of relapse / resistance?

• It is imperative to select a more homogenous patient population for accurate understanding of the compact of the new drug.

• If the drug fails to deliver responses – is the target still invalid?

• If active – than how much and at what cost to the patient (toxicity) and to our society (economic)?