Relapse after Autotransplantation for Myeloma

- Defining the problem
- Identifying Opportunity

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Medical College of Wisconsin
• Epidemiology of Relapse
• Post Relapse Survival
• Biology of Relapse
• Who does not relapse? Why?

• Preventing and Treating Relapse – the clinical opportunities
MYELOMA SURVIVAL Has Improved Over Time

Current 10 yr survivor fraction – May be 50% for younger patients?
The best median PFS with modern induction and maintenance – is about 46 mo

### Recent Studies

<table>
<thead>
<tr>
<th>Recent Studies</th>
<th>Agent</th>
<th>Median TTP/PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 100104</td>
<td>Lenalidomide</td>
<td>46 mo</td>
</tr>
<tr>
<td>IFM Attal et al</td>
<td>Lenalidomide</td>
<td>41 mo</td>
</tr>
<tr>
<td>HOVON-GMMG</td>
<td>Bortezomib</td>
<td>35 mo</td>
</tr>
<tr>
<td>MRC IX</td>
<td>Thalidomide</td>
<td>30 mo</td>
</tr>
</tbody>
</table>
“The Modern Triple Sequence”
Induction AutoHCT and Maintenance

- Randomized trials – Achievement of VGPR/CR or better
- Emerging data – PCR or Multicolor Flow based remissions

- [INITIAL] 3 Drug Induction
- [CONSOLIDATE] Consolidation with Transplant
- [ONGOING THERAPY] Maintain with Len or Bortezomib
- [RELAPSE MONITORING] TREATMENT of RELAPSE
  - Biochemical or Clinical

Better Induction VGPR before ASCT

Second AHCT ALLO HCT Other Immune

MRD directed? When to stop? Implications of prolonged therapy

Are all Relapses the same?
Survival After Relapse from Upfront Auto HCT

Mayo Clinic Proceedings 2004; 79:867-874

- Median response duration (mo):
  - First: 10
  - Second: 6
  - Third: 4
  - Fourth: 2
  - Fifth: 1
  - Sixth: 0.5

- Median OS to salvage therapy - 1.5 years (b/w 1985-98)

IMWG International survey ASCO 2012, Durie et al
- Median PFS and OS after relapse:
  #1: 13 mo and 35 mo

<table>
<thead>
<tr>
<th>Salvage Regimen</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58%</td>
</tr>
<tr>
<td>2</td>
<td>45%</td>
</tr>
<tr>
<td>3</td>
<td>30%</td>
</tr>
<tr>
<td>4</td>
<td>15%</td>
</tr>
</tbody>
</table>

Survival After Relapse from Upfront Auto HCT:

- 2 yr Survival after relapse:
  - 1995-99: 58% (53-62%)
  - 2000-04: 65% (62-68%)
  - 2005-10: 72% (69-74%)
Dual (IMID and Proteasome Inhibitor) Refractory Disease

- Median EFS: 5 months
- Median OS: 9 months

EFS and OS in Patients Relapsing and Refractory to Bortezomib and Thalidomide or Lenalidomide

EFS and OS are poor in dual refractory disease

Genomic Instability
Immortalization
Resistance to apoptosis
Abnormal Localization
Failure of immune surveillance
Secondary genetic changes

Biology of Relapse
Multi-clonal pre MM

Mechanisms underlying this equilibrium

Morgan et al 2012
Darwinian Process

Nature Reviews | Cancer

Morgan et al 2012
Correlating Clinical and Biologic Data

- Clinical Features of Relapse
  - diminishing responses, shortening durations of responses and emerging resistance and refractoriness

- Underlying Biology?

- Recent CGH studies –

- Darwinian Competition

- Clonal tides

• Competition between sub clones over time in the same patient
Clonal Evolution of MM relapse

- Genetically Stable – 35%
- Linear Evolving – 22%
- Heterogeneous clones – 43%

Keats et al Blood 2012
Rapid debulking (AHCT)

Maintenance

STASIS or Punctuated Equilibrium

Nature Reviews | Cancer

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Clonal architecture in MM at diagnosis and relapse

MPC – Myeloma Propagating Clones

Tumor initiating cell

Ancestral clones

Diagnostic Clone(s)

 Diagnostic dominant and minor clones

Treatment

Subclones with unique nonlinear branching mutations

Subclones with linearly derived mutations

= Dominant clone

= Minor clone

Potential of Relapse Clones

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Bahlis N J Blood 2012;120:927-928
Does treatment impact the biology of Relapse?

• Comparison of paired diagnosis and relapse DNA samples by SNP array

• 2 distinct patterns of sub-clonal evolution in MM
  – Linear pattern (2/3)
  – Nonlinear pattern (1/3) –
    • dominant subclone eliminated by therapy but minor subclone survived and expanded at relapse.
    • in Bortezomib treated patients and those with CR/VGPR

– Bortezomib-based treatment:
  • eliminate the ‘driver’ mutation but lead to persistent subclones that are a reservoir for relapse.

Magrangeas et al, Leukemia 2012
*Patients were stratified by $\beta_2$-microglobulin and albumin levels.

IFM2005 / 01, VD vs. VAD, Phase III
Should Biology inform treatment?

**QUESTIONS:**
- Continuous treatment → selection of aggressive clones when multiple sub-clones are present?
- Treatment Implications for maintenance?
- Retreatment with previously tried agents is warranted as a previous clone re-emerges?
- Combination chemotherapy for multi-clonal aggressive relapse?
- Avoiding genotoxic therapy to avoid exerting selection pressure in the background of clonal heterogeneity?

**“Molecular Mayhem at relapse “**
- Pathways known
  - ERK, NFkB, PI3K
- Some of them have specific directed MM therapy in trials
- Disruption of protein degradation pathway is our most advanced targeted therapy at this time
- Molecular classification
- Or Molecular Diagnosis?
Current Treatment of Relapse
**RELAPSED MYELOMA -- RECENT STUDIES**

VTD vs. TD combination in first relapse after Auto HCT

<table>
<thead>
<tr>
<th>Other agents in Relapsed Disease</th>
<th>ORR, %</th>
<th>TTP/PFS, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Len + dex MM-009[^1]</td>
<td>61</td>
<td>11</td>
<td>35[^5]</td>
</tr>
<tr>
<td>Len + dex MM-010[^2]</td>
<td>60</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Bortezomib APEX[^3]</td>
<td>43</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Vdox MMY-3001[^4]</td>
<td>44</td>
<td>9</td>
<td>NE</td>
</tr>
</tbody>
</table>

Salvage second AutoHCT at Relapse
(stratified by Time from first Auto HCT to Relapse)

Probability of OS, %

Years

0 1 2 3 4 5 6 7 8 9

0 10 20 30 40 50 60 70 80 90 100

<36 months

>36 months

(HR 1.91, P = 0.02)

(Source: Tsz11_7) MM09-02-11_23.ppt
Salvage Second Allo or Auto HCT

Relapse/Progression (95% CI):
@ 1 yr: allo 72% (64-79), auto 53% (44-61)
@ 3 yrs: allo 80% (73-86), auto 84% (76-90)
@ 5 yrs: allo 83% (77-89), auto 91% (85-96)

(Source: Txz11_8) MM02-01-11_11.ppt
Who does not Relapse?
LONG TERM CR – some never relapse

No further relapse
After 11 years in CR

$P = .00001$

CR (n=84)

nCR (n=66) + VGPR (n=54) + PR (n=114)

SD (n=12) + PD (n=14)

SUSTAINED CR vs. NO CR vs. Unsustained CR

Landmark Analysis of TT 1 trial

Long survival without CR—patients with prior MGUS /SMM
Importance of immune reconstitution
Flow Analysis of plasma cell immune paresis

Hoering A et al. Blood 2009;114:1299-1305
Long term survival → freedom from PROGRESSION not RELAPSE

• Genomic/genetic classification of myeloma – clones one can live with vs. those that need to be eradicated

• Immune Mechanisms that underlie MGUS like states (post treatment) – clonal equilibrium

• Avoid: emergence of resistant clones or prevent factors that promote genomic instability
Those at highest risk of early Relapse
New Agents and Relapsed MM
Elotuzumab

• Humanized IgG\textsubscript{1} mAb targeting human CS1, a cell-surface glycoprotein\textsuperscript{[1,2]}
• CS1 highly expressed on > 95% of MM cells\textsuperscript{[1-3]}
  – Lower expression on NK cells
  – Little to no expression on normal tissues

Primary mechanism of action: NK cell-mediated ADCC against myeloma cells\textsuperscript{[1,2]}

CS1 is highly and uniformly expressed on multiple myeloma and normal plasma cells and

- Restricted expression on NK cells
  - Elotuzumab binds to the CS1 receptor of the target cell resulting in target cell death
  - MOA observed to be mainly NK-mediated ADCC

**ELOTUZUMAB + LENALIDOMIDE**

<table>
<thead>
<tr>
<th>Response</th>
<th>Elotuzumab 20 mg/kg (n = 37)</th>
<th>Total (N = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥ PR), n (%)</td>
<td>27 (73)</td>
<td>60 (82)</td>
</tr>
<tr>
<td>▪ Pts with ≥ 2 previous therapies</td>
<td>13 (65)</td>
<td>30 (75)</td>
</tr>
</tbody>
</table>
## Carfilzomib

<table>
<thead>
<tr>
<th>Trial</th>
<th>N*</th>
<th>Population</th>
<th>Previous Lines, n</th>
<th>ORR, %</th>
<th>MR/SD%</th>
<th>Median TTP, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>003-A0[1]</td>
<td>39</td>
<td>Relapsed/refractory</td>
<td>&gt; 2</td>
<td>18</td>
<td>8/41</td>
<td>6.2</td>
</tr>
<tr>
<td>004 (Bz exposed)[3]</td>
<td>35</td>
<td>Relapsed/refractory</td>
<td>1-3</td>
<td>21</td>
<td>12/35</td>
<td>8.1</td>
</tr>
<tr>
<td>004 (Bz naive)[4]</td>
<td>59</td>
<td>Relapsed/refractory</td>
<td>1-3</td>
<td>42</td>
<td>17/22</td>
<td>8.3 NR</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td></td>
<td></td>
<td>52</td>
<td>12/15</td>
<td></td>
</tr>
<tr>
<td>006 (combo with len/dex)[5]</td>
<td>50</td>
<td>Relapsed/refractory</td>
<td>1-3</td>
<td>78</td>
<td>2/8</td>
<td>--</td>
</tr>
</tbody>
</table>

*Evaluable for response.

Neuropathy from phase II experience
9.6% grades 1/2 and 1.4% grade 3

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# PX-171-006: Phase II Carfilzomib Plus Len/Dex in Relapsed/Refractory MM

Carfilzomib 20/27 mg/m² IV*  
D1/D2  
 Week 1  
D8/D9  
 Week 2  
D15/D16  
 Week 3  
D22  
 Week 4: rest  

<table>
<thead>
<tr>
<th>Week</th>
<th>Carfilzomib</th>
<th>Dexamethasone</th>
<th>Lenalidomide D1-D21</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20/27 mg/m²</td>
<td>40 mg/d PO</td>
<td>25 mg/d PO</td>
</tr>
<tr>
<td>2</td>
<td>20 mg/m²</td>
<td>D8</td>
<td>D1-D21</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>D15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>D22</td>
<td></td>
</tr>
</tbody>
</table>

*20 mg/m² cycle 1 days 1 and 2 only, 27 mg/m² thereafter

### Response (N = 51)

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/nCR</td>
<td>12 (24)</td>
</tr>
<tr>
<td>VGPR</td>
<td>9 (18)</td>
</tr>
<tr>
<td>PR</td>
<td>19 (37)</td>
</tr>
<tr>
<td>MR</td>
<td>1 (2)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (6)</td>
</tr>
<tr>
<td>ORR</td>
<td>40 (78)</td>
</tr>
</tbody>
</table>

# Pomalidomide

- **IFM 2009-02**
- **Median follow-up: 11.3 months (similar in the 2 arms)**

## Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Arm A: 21/28 days (n = 43)</th>
<th>Arm B: 28/28 days (n = 41)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥ PR), %</td>
<td>35.0</td>
<td>34.0</td>
<td>34.5</td>
</tr>
<tr>
<td>- CR, n</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>- VGPR, n</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>- PR, n</td>
<td>13</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>Median time to first response, mos</td>
<td>2.7</td>
<td>1.1</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Median duration of response, mos</strong></td>
<td><strong>10.5</strong></td>
<td><strong>7.2</strong></td>
<td><strong>8.1</strong></td>
</tr>
<tr>
<td>- ≥ 1 yr in responders, %</td>
<td>47.5</td>
<td>36.0</td>
<td>37.5</td>
</tr>
</tbody>
</table>

NK based strategy vs. MM?- An Anecdote

Free Lambda LC

Rel #1
- CVRD x 6 -> VGPR
- At HCT – Marrow 20% PC
- CR -> BTZ maintenance

Rel #2
- VDPACE x 2 -> PR
- 6 mo marrow & FLC - negative
- VRD maintenance ->

Upfront VTD x 4 + Auto HCT

Haplo HCT with post HCT NK cell DLI

Thakar M et al

Priorities in the setting of MM relapse

**PREVENTION OF RELAPSE AFTER AUTO HCT**

- Genetics of relapse clones after modern triple phase sequence – design ancillary protocols to current trials
- Achieve the 2 Mechanisms of long term OS:
  - sus-CR or a “secondary“ MGUS like state
  - Avoid a los-CR
- Cellular therapies to reverse MM specific immune paresis
- IMIDs / Elotuzumab and PD-1-PDL axis
- Clinical priority:
  - High risk patients
  - Allogeneic strategies revival
Clinical Priorities

RELAPSE AFTER AUTO HCT – NEED FOR BETTER TREATMENT

- Target First Relapse after AutoHCT
  - Treat as a priority event and design unique trials
  - Re-induce with combination and debulk vs. sequential therapies
  - Novel conditioning trials for AutoHCT
  - Allo HCT and maintenance
  - Genomics of relapse – same clone vs. subclone vs. new clone. How do we distinguish and choose therapy?

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