Role of Stem Cell Transplantation in Multiple Myeloma: The Changing Landscape

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Why Transplant in the Era of Novel Therapy?

- Safe (TRM <2%)
- Highest CR rates before novel agents
- Higher CR rates when used in combination with novel agents
- Mature data on the durability of response
- Longer PFS and better QOL in patients receiving Auto HCT early
- Comparable cumulative cost

<table>
<thead>
<tr>
<th></th>
<th>G-CSF Mob. + ASCT</th>
<th>Revlimid + Velcade + Dex (6 cycles)</th>
<th>Velcade + Dex (6 cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>155K</td>
<td>150K</td>
<td>126K</td>
</tr>
</tbody>
</table>
AutoSCT in Outpatient Setting

- CVC insertion
- Fluid infusion
- HDC administration
- Rest

- HPC infusion

- Supportive care management for the aplastic phase

Outpatient clinic
Multiple Myeloma Treatment Lines in Transplant-Eligible Patients

Current Paradigm

**Induction**
- Bz/Dex
- Bz/Dex/Dox
- Bz/Thal/Dex
- Len/Dex

**Consolidation**
- SCT

**Maintenance**
- Observation
  - Thal
  - Thal/Pred
  - Lenalidomide

**Relapsed**
- Bz
- Bz/Liposomal Dox
- Len/Dex
- Carfilzomib
- Bendamustine

Risk Stratification?

Early Myeloablative Therapy in Autologous BM Transplant Patients

**IFM90**
- Overall Survival (%)
- Treatment (mo)
- Transplant
- Conventional
- $P = 0.03$

**MRC7**
- Overall Survival (%)
- Treatment (mo)
- Transplant
- Conventional
- $P = 0.04$

THE TRANSPLANT QUESTIONS FOR 2012

• Focusing on reducing burden of treatment
  – Does everybody need triple therapy induction?
    • Would a doublet (Rd or Vd) be sufficient for standard risk disease?
    • Is VRD the new standard?
      – No randomized trial data available
  – Optimal duration of induction?
    • 2 cycles vs 4 cycles vs “best response”?

• Define Timing of SCT
  – Is SCT optional for patients achieving a CR?
  – Should salvage SCT be offered to all relapsing patients SCT naïve or not?

• Focusing on improving therapy
  – Incorporating new agents into conditioning regimens
  – Reducing morbidity
  – Preventing relapse: Maintenance Therapy
Tumor Burden Reduction

• CR or VGPR has emerged as the most important factor associated with a prolonged progression-free survival (PFS) and overall survival (OS).

• The sensitivity to the initial chemotherapy, measured by the M-protein reduction at the time of transplantation, is the most important predictor of residual disease after ASCT.

Lahuerta, JCO 2008
Luskin et al 4134

- VRD → AutoSCT
- At 100 days post-ASCT, 33% showed improvement in disease response.
- PFS at 12 months post-ASCT is 85%
# Randomized Phase III HOVON-65/GMMG-HD4 Trial

<table>
<thead>
<tr>
<th>Response Level</th>
<th>VAD (%) N=414</th>
<th>PAD (%) N=413</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>2</td>
<td>7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nCR</td>
<td>5</td>
<td>11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VGPR</td>
<td>14</td>
<td>42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PR</td>
<td>54</td>
<td>78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After HDM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>9</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nCR</td>
<td>15</td>
<td>31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VGPR</td>
<td>36</td>
<td>62</td>
<td>&lt;0.001</td>
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<tr>
<td>PR</td>
<td>75</td>
<td>88</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Sonneveld, JCO2012
## Phase 3 PETHEMA/GEM study

<table>
<thead>
<tr>
<th></th>
<th>VTD (n=130)</th>
<th>TD (n=127)</th>
<th>VBMCP/VBAD/B (n=129)</th>
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<tbody>
<tr>
<td><strong>CR</strong></td>
<td>35%</td>
<td>14%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>56.2 mos</td>
<td>28.2 mos</td>
<td>35.5 mos</td>
</tr>
<tr>
<td><strong>After HDM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>46%</td>
<td>24%</td>
<td>38%</td>
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</tbody>
</table>

*Rosinol, Blood 2012*
Melphalan/Prednisone/Lenalidomide (MPR) vs MEL200/ASCT Following Lenalidomide/Dexamethasone (Ld) Induction

Primary end point: PFS

Consolidation

MPR (n=202)
- Melphalan: 0.18 mg/kg/d, days 1–4
- Prednisone: 2 mg/kg/d, days 1–4
- Lenalidomide: 10 mg/d, days 1–21 q 28 days x6

Tandem MEL200
- ASCT
- stem cells mobilized with cyclophosphamide + G-CSF

Progression Free Survival

49.4% Reduced Risk of Progression

Median follow-up 26 months

<table>
<thead>
<tr>
<th></th>
<th>2-years PFS</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEL200</td>
<td>73%</td>
<td>Not reached</td>
</tr>
<tr>
<td>MPR</td>
<td>54%</td>
<td>25.26 mos</td>
</tr>
</tbody>
</table>

HR 0.506
P = 0.0002

MPR, melphalan-prednisone-lenalidomide; MEL200, melphalan 200 mg/m²; PFS, progression free survival; HR, hazard ratio; mos, months
Overall Survival

Median follow-up 26 months

<table>
<thead>
<tr>
<th>Months</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>5</td>
<td>0.99</td>
</tr>
<tr>
<td>10</td>
<td>0.98</td>
</tr>
<tr>
<td>15</td>
<td>0.96</td>
</tr>
<tr>
<td>20</td>
<td>0.94</td>
</tr>
<tr>
<td>25</td>
<td>0.92</td>
</tr>
<tr>
<td>30</td>
<td>0.90</td>
</tr>
<tr>
<td>35</td>
<td>0.88</td>
</tr>
<tr>
<td>40</td>
<td>0.86</td>
</tr>
<tr>
<td>45</td>
<td>0.84</td>
</tr>
</tbody>
</table>

MPR, melphalan-prednisone-lenalidomide; MEL200, melphalan 200 mg/m²; OS, overall survival; HR, hazard ratio

2-years OS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEL200</td>
<td>90%</td>
</tr>
<tr>
<td>MPR</td>
<td>87%</td>
</tr>
</tbody>
</table>

HR 0.678

P = 0.19
E4A03: Landmark Analysis at Median Follow-up of 36 mo

431 patients alive at 4 cycles

- Off therapy at 4 cycles
  - 183 patients
    - No transplant
      - N=93
        - (median age 68)
    - Transplant
      - N=90
        - (median age 57)

- Primary therapy beyond 4 cycles
  - 248 patients
    - Ld
      - N=140
        - (median age 66)
    - LD
      - N=108
        - (median age 65)

Rajkumar SV et al. The Lancet Oncology, Volume 11, Issue 1, Pages 29 - 37, January 2010
Outcomes in pts Age <65

Progression Free Survival

Overall Survival
Summary: Conventional Chemotherapy vs. Single Auto HCT

- OS benefit in at least 2 large, randomized trials
- Novel agents (lenalidomide, bortezomib) are not curative
- RCT incorporating the novel agents (VTD) as induction and/or consolidation with auto HCT are showing significant improvement in outcome (Harousseau et al. JCO 2010; Cavo et al. Lancet 2010)
- NCCN: Category 1 evidence supports proceeding straight to auto HCT after induction therapy
Thal Dex Maintenance: Brazilian Multiple Myeloma Study Group (BMMSG/GEMOH)

- VAD induction → MEL200 ASCT
- Randomize to Dex (n=52) or Thal/dex (n=56; 200 mg daily) for 12 mos or until ds progression
- Median follow-up 27 months
- ITT analysis; 2-year PFS of 30% vs. 64% (p=0.002),
- In patients <VGPR, the 2-yr PFS 19% vs. 59% (P=0.002)
- OS 70% vs. 85% (p=0.27)

Mailono, AJH 2012
Role of Consolidation Therapy Hypothesis

Incorporation of new agents as post transplant consolidation will improve EFS compared to consolidation with second autologous HCT.
BMT CTN 0702
A Trial of Single Autologous Transplant with or without RVD Consolidation versus Tandem Transplant and Maintenance Therapy.

STaMINA
Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents
BMT CTN 0702: SCHEMA

Register and Randomize

MEL 200mg/m²

Lenalidomide* Maintenance

VRD x 4*

Lenalidomide Maintenance**

MEL 200mg/m²

Lenalidomide 15 mg daily x 3 years

* Bortezomib 1.3mg/m² days 1, 4, 8, 11
  Lenalidomide 15mg days 1-15
  Dexamethasone 40mg days 1, 8, 15

**Lenalidomide 15 mg daily x 3 years
Summary

• High dose melphalan with autologous stem cell support remains the standard of care for consolidation therapy for patients with chemosensitive disease.

• Current therapy with high dose melphalan followed by maintenance therapy results in more than 70% major responses and median remission durations of around 3.5-4 years.

• Moving forward minimizing toxicities, developing more effective conditioning regimens and better risk stratification will allow us to provide each patient with the best chance of a long life with myeloma control, good quality of life with the least treatment burden.
MDACC 2012

SCT and Cellular Therapies

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We Thank
Our Patients and their Families