A Single Autologous Stem Cell Transplant (ASCT) followed by two years of post-transplant therapy is safe in Older Recently Diagnosed Multiple Myeloma (MM) Patients. Preliminary Results from the Prospective Phase II Trial (NCT01849783)

Kalyan Nadiminti, MBBS, Lindsay Dozeman, Allyson Schultz, Sheila Ouverson, Fenghuang Zhan, MD, PhD, Margarida Silverman, MD, Guido J. Tricot, MD, PhD and Yogesh Jethava, MBBS, FRCPath, MRCP

Kalyan Nadiminti, MBBS
4/13/18
Within the past twelve months, I have not had any financial relationships with the manufacturers of health care products
Background

Blood and Marrow Transplant Program

• The median age at diagnosis of MM patients is around 70
• Treatment and survival in patients has evolved and improved in the last decade with the advent of novel therapies and improved supportive care
• Autologous stem cell transplant (ASCT) remains a crucial backbone treatment modality
  – although there is still a debate about the timing and number of transplant (upfront Vs delayed) and single Vs Tandem
• Most prospective studies restricted patients < 65 years
• Benefit of transplant in elderly patients mostly in retrospective studies
• One study also suggested economic benefit of upfront transplant
Background
Blood and Marrow Transplant Program

• The current standard of treatment for eligible MM patients is ASCT after initial induction chemotherapy
• Also, recent studies have confirmed survival advantage of lenalidomide maintenance post ASCT
  – IFM 2005-02 study randomized lenalidomide 10-15 mg/d) or placebo until disease progression or unacceptable side effects
  – CALGB 100104 study randomized patients to continue on lenalidomide 10-15 mg/d or placebo maintenance until progression or intolerance
• Both studies and a meta-analysis showed PFS and PS benefit of lenalidomide maintenance post ASCT
**Introduction**

**Blood and Marrow Transplant Program**

- Standard preparative regimen for ASCT consists of Melphalan 200 mg/m2
- Many attempts to improve the efficacy of preparative regimen were unsuccessful due to increased toxicities and no added benefit
- We previously reported the safety and efficacy of incorporating novel agents as part of preparative regimen
  - VTD- Mel 200 mg/m2 (Bortezomib, Thalidomide and Dexamethasone) in patients *mostly younger than 65 years*
  - This study showed deep responses and higher rates of MRD negativity at 1 year analysis
- With these results we attempted the efficacy and safety of this novel preparative regimen in elderly patients in a prospective study
Study
Blood and Marrow Transplant Program

• Regimen was as follows
  – Bortezomib 1mg/m2 IV Bolus on days -4, -1, +2 and +5
  – Thalidomide 100 mg/d day -4 to day+ 5
  – Dexamethasone 20 mg/d day -4 to -1 and day +2 to +5
  – Melphalan 100 mg/m2 OR (70mg/m² if > age 70 or creatinine > 2.0 mg/dl ) on days -4 and -1
  – PBSC infusion 24 hrs post Melphalan on day 0

• Maintenance
  – **Year 1 (28 day cycles x 12):** Bortezomib 1.0 mg/m2 days 1, 4, 15, 18, Thalidomide 100mg daily, Dexamethasone 20mg days 1-4 and 15-18.
  – **Year 2 (28 day cycles x 12):** Bortezomib 1.0 mg/m2 days 1, 4, 15, 18, Cyclophosphamide 500mg days 1 and 15, Dexamethasone 20mg days 1-4 and 15-18.
Patients and methods
Blood and Marrow Transplant Program

- A total of 41 eligible patients above the age 65 were prospectively enrolled in the IRB approved phase II trial beginning in June 2013.
  - Average age: 71
  - 19 female, 22 male

- Stem cells were collected after 1 cycle of DPACE chemotherapy

- After an induction chemotherapy and stem cell collection, ASCT was performed with the preparative chemotherapy consisting of VDT-Melphalan 200mg/m2

- Early after engraftment, patients were started on maintenance for 2 years with triple agent therapy for 2 years
End points
Blood and Marrow Transplant Program

• Primary end point is PFS

• Secondary end points include frequency of severe toxicities, ICU admissions, and percentage of patients able to complete the full course of maintenance
Results

Blood and Marrow Transplant Program

• Here we report the 100 day toxicity and early post-transplant response data
• Of the 41 patients enrolled, 37 patients had at least day 100 follow up post-transplantation and were included in this analysis. Six have been removed from study due to relapse (N=2), development of acute leukemia (N=1), failure to collect stem cells (N=1) or failure to comply with therapy (N=2)
• Toxicity and best response were assessed at day 100
• Median age was 68 (range: 65 to 75).
• Median follow up was 21 months (3.5 months – 3.7 years)
Results
Blood and Marrow Transplant Program

• Median time to ANC and platelet engraftment was 11 and 17 days, respectively

• 18 patients achieved a stringent CR (sCR) by day 100 restaging (49%)

• There was one death within day 100 related to candida sepsis

• Only 2 patients were re-hospitalized within 100 days

• Major non-hematologic toxicities ≥ grade 3 were related to infections (25%), diarrhea (19%) and mucositis (11%)

• Thirty-five patients started maintenance therapy. Median time to start post-transplant therapy was 66 days (range: 42 to 174 days)
Results
Blood and Marrow Transplant Program

Best responses achieved

<table>
<thead>
<tr>
<th>Best Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>18(49%)</td>
</tr>
<tr>
<td>CR</td>
<td>2(5%)</td>
</tr>
<tr>
<td>PR</td>
<td>12(32%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>4(11%)</td>
</tr>
<tr>
<td>Unable to assess</td>
<td>1(3%)</td>
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</tbody>
</table>

Best Response
100 Days Post-Transplant

<table>
<thead>
<tr>
<th>Best Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>49%</td>
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<tr>
<td>CR</td>
<td>5%</td>
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<tr>
<td>Unable to assess</td>
<td>3%</td>
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Cytogenetics

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>N(%)</th>
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<tbody>
<tr>
<td>Standard risk</td>
<td>22(59%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>9(24%)</td>
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<tr>
<td>High risk</td>
<td>6(16%)</td>
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## Toxicities summary

Blood and Marrow Transplant Program

<table>
<thead>
<tr>
<th>Toxicities &gt; grade 3</th>
<th>N(%)</th>
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</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>37(100%)</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>37(100%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>37(100%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>37(100%)</td>
</tr>
<tr>
<td>Infection</td>
<td>10(25%)</td>
</tr>
<tr>
<td>diarrhea</td>
<td>7(19%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>6(16%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>4(11%)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Readmission within 100 days</th>
<th>N(%)</th>
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<tbody>
<tr>
<td></td>
<td>2(5%)</td>
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**Discussion**

Blood and Marrow Transplant Program

- This is the first trial to prospectively evaluate the feasibility of combined intensified preparative regimen in upfront ASCT followed by two years of maintenance using triple agent therapy (VTD/VCD) in elderly MM patients > 65 years.
- Toxicity and mortality were not increased compared to the younger patients (median age 59) receiving a similar regimen in our institution which was reported earlier.
Discussion
Blood and Marrow Transplant Program

• Although it is too early to comment on the efficacy of this approach, we are encouraged by the high frequency of sCR, early after transplantation
• Tolerability and efficacy of triple maintenance therapy in older patients will be evaluated in this study
• Recent data suggests MRD negativity and depth of response predicts longer disease free survival
• Improving ASCT efficacy can improve outcomes
• Role of tandem transplants is still being debated although recent data again show benefit of ASCT, especially in higher risk disease
Discussion
Blood and Marrow Transplant Program