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Bortezomib and high dose melphalan conditioning for stem cell transplantation for AL amyloidosis: a pilot study

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Treatment with high dose intravenous melphalan followed by autologous stem cell transplantation (HDM/SCT) can induce hematologic responses, organ responses and lead to improvement in survival in selected patients with AL (immunoglobulin light chain) amyloidosis. The depth of hematologic response, in particular the achievement of complete hematologic response (CR), has been shown to be predictive of clinical response, quality of life and improvement in survival. The median survival of patients achieving hematologic CR after HDM/SCT in a landmark analysis of patients alive at 1 year following treatment exceeds 10 years compared to 50 months for those not achieving a hematologic CR.

The proteasome inhibitor bortezomib (Bz) has been approved for treatment of myeloma. Recent studies demonstrate high response rates when Bz is used in combination with oral melphalan and prednisone. While the mechanism of action is not completely understood, Bz sensitizes myeloma cells, in vitro, to DNA-damaging agents such as melphalan, and overcomes chemoresistance. It also acts upon the bone marrow microenvironment, inhibiting nuclear factor-κB activation in bone marrow stromal cells, leading to a reduction in interleukin-6 production and enhanced apoptosis of myeloma cells. Recently, Bz has been incorporated into HDM conditioning for SCT in myeloma. Pre-clinical and phase I/II data have suggested that the optimal timing of administration of a single dose of bortezomib is 24 hours after melphalan.

Because hematologic CR is a critical determinant of treatment outcome following HDM/SCT, we hypothesized that the addition of Bz to HDM/SCT could increase hematologic CR rates in patients with AL amyloidosis. This hypothesis led us to conduct a prospective pilot feasibility study of Bz-HDM/SCT for the treatment of AL amyloidosis (ClinicalTrials.gov: NCT00790647). The objective of this trial was to determine whether the addition of Bz to HDM/SCT has the potential to improve hematologic CR rates in patients with AL amyloidosis.
undergoing HDM/SCT. Additional objectives were to evaluate the tolerability of the combination and its impact upon clinical responses.

This clinical trial was approved by the Institutional Review Board of the Boston University Medical Campus. Eligibility criteria for participation on this clinical trial were as described in previous HDM/SCT protocols\(^1\). Patients with grade 3 peripheral sensory neuropathy from AL amyloidosis were not eligible to participate on this trial. Peripheral blood stem cells were mobilized with G-CSF, and a minimum of 2.5 \(\times\) 10\(^6\) CD 34+ cells/kg was required for transplantation. Bz was administered at 1 mg/m\(^2\) on D -6, D -3, D +1, and D +4 and HDM was administered at 140 or 200 mg/ m\(^2\) in two divided doses on D -2 and D -1, depending upon age and co-morbidities. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3, was used to grade adverse events. Treatment-related mortality was defined as death occurring from the time of stem cell mobilization through day +100 following HDM/SCT. Hematologic and clinical responses were assessed 6 and 12 months after HDM/SCT. The response criteria for hematologic and clinical/organ response used were standards defined by the consensus opinion from the 10\(^{th}\) International Symposium on Amyloid and Amyloidosis\(^10\).

Ten subjects with AL amyloidosis were enrolled in this clinical trial from October 2008 to November 2009. The median age was 65 years (range, 46 to 68); and 60% were men. The median number of organs involved was 2 (range, 1 to 4). There were 2 patients (20%) with cardiac involvement; both had elevated BNP (B-type natriuretic peptide) and troponin I levels (Mayo clinic cardiac stage III)\(^11\). The median BNP level for all patients was 84 pg/mL (range, 8-325). Two patients (20%) had received prior treatment with 2 cycles of bortezomib and dexamethasone. Other patient characteristics are shown in Table 1.
Of the 10 subjects enrolled, one was removed from the study prior to treatment because of cardiac arrhythmias during stem cell collection that precluded HDM/SCT. This patient subsequently underwent orthotopic heart transplantation followed by HDM/SCT. Of the 9 remaining subjects on the trial, 8 received 200 mg/m² of HDM and 1 received 140 mg/m² due to age > 65 years. In this pilot study, there was no treatment-related mortality. The median times to neutrophil and platelet engraftment were D +10 and D +14 after SCT, respectively. One of the 9 subjects developed grade 4 mucositis, one developed grade 3 renal failure not requiring dialysis, and three developed grade 3 infectious complications (enterococcus urinary tract infection, clostridium difficile colitis, and influenza A pneumonia).

Hematologic responses occurred in 89% of treated subjects (n=8/9), of which 6 (67%) were hematologic CRs. Thus, by intention-to-treat, 80% (n=8/10) had a hematologic response to treatment. Only 1 treated subject developed worsening of hematologic parameters, necessitating additional treatment. There have been no hematologic relapses at a median follow-up of 23 months (range, 18-31). Seventy-eight % of treated patients (n=7/9) had an organ response at 1 year following Bz-HDM/SCT, 6 with renal and 1 with hepatic response (Figure 1). All subjects are alive and well after a median follow-up of 29 months from the time of diagnosis and 23 months from the enrollment on study.

In conclusion, this pilot study demonstrates that the addition of Bz to the conditioning regimen for HDM/SCT is feasible and well-tolerated by patients with AL amyloidosis. The combination resulted in no increase in adverse events over those typically seen with HDM alone. Furthermore, the combination produced a high rate of hematologic and organ responses. Although this pilot study is small in highly select patients, the CR rate of 67% of treated patients compares favorably with that of 40% seen in prior series using melphalan alone for
conditioning. This suggests that there may be additive or synergistic activity of Bz and melphalan, due to the activity of Bz as a chemosensitizer and its effect on the bone marrow microenvironment. We plan a second clinical trial using Bz for initial induction therapy as well as incorporating it into the conditioning regimen. Based upon the results of these two studies, the regimen with superior phase II results will be compared to a standard melphalan-based SCT in a randomized phase III study, with the goal of determining whether the addition of Bz leads to a higher rate of hematologic and clinical responses, and better progression-free and overall survival.

Key words
AL amyloidosis, stem cell transplantation, bortezomib

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Authorship Contributions
VS designed research, performed research, analyzed data, wrote the manuscript. KQ designed research, performed research, analyzed data and critically reviewed the manuscript. JMS performed research, analyzed data and critically reviewed the manuscript. NTA performed research, analyzed data and critically reviewed the manuscript. DCS designed research, performed research, analyzed data, and critically reviewed the manuscript.

Disclosure of Conflicts of Interest
The authors declare no competing financial interests.

References:

Table 1:

Patient Characteristics

<table>
<thead>
<tr>
<th>Feature</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>65 (46-68)</td>
</tr>
<tr>
<td>Patients ≥65 yrs, number (%)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Performance status, median (range)</td>
<td>1 (0-1)</td>
</tr>
<tr>
<td>No. organs involved, median (range)</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>1 organ, n (%)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>2 organs, n (%)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>≥3 organs, n (%)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Types of organs involved</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Liver/GI</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>% BM plasma cells, median (range)</td>
<td>5 (5-25)</td>
</tr>
<tr>
<td>Light chain isotype</td>
<td></td>
</tr>
<tr>
<td>Kappa, n (%)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Lambda, n (%)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Median time from diagnosis to SCT (months) (range)</td>
<td>4.8 (2.4-7.3)</td>
</tr>
<tr>
<td>Dose of melphalan, n (%)</td>
<td></td>
</tr>
<tr>
<td>200 mg/m²</td>
<td>8 (80)</td>
</tr>
<tr>
<td>140 mg/m²</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Follow-up (months), median (range)</td>
<td>23 (18-31)</td>
</tr>
</tbody>
</table>
Figure Legends:

Renal response with improvement in urine protein excretion at 1 year after Bz-HDM/SCT
Renal response at 1 year following Bz-HDM/SCT

Urine protein excretion, g/24hr

Time

Pre SCT

1 year after SCT

Patient 1

Patient 2

Patient 3

Patient 4

Patient 5

Patient 6