



A Randomized Phase I trial of Melphalan + Bortezomib as Conditioning for Autologous Transplant for Myeloma: The Effect of Sequence of Administration.



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Abstract:

Background: High dose therapy and autologous transplant (HDT) clearly benefits many patients with myeloma, but the addition of other chemotherapeutics or TBI to high dose melphalan (HDM) does not improve outcomes. Bortezomib (B) is a proteasome inhibitor that synergizes with chemotherapy due to its effects on DNA repair enzymes. Recent data has shown that B upregulates the anti-apoptotic protein MCL-1, which would suggest that the sequence of administration may be critical to the combination of B and HDM. We hypothesize that B followed by M is inferior to M followed by B. To test this hypothesis, we designed a randomized phase I trial combining escalating doses of B and Melphalan 200 mg/m² (Mel200) in order to determine the toxicity, optimal dose and sequence of administration.

Methods: Patients were randomized to receive either B 24 hours before Mel 200 (ARM A) or B 24 hours after Mel 200 (ARM B). Doses for B escalated from 1.0mg/m² up to 1.6mg/m² as defined using the Escalation with Overdose Control (EWOC) method, a Bayesian phase I design. Patients eligible for the study were required to have achieved no better than a PR following induction therapy, and to have measurable disease in the bone marrow. Enrolled patients underwent BM aspirate on day -4 (before B) and day 0 (before PBSC infusion). Bone marrows were tested for annexin V staining, and myeloma cells were sorted for protein analysis. We compared the increase in annexin V and PI staining from the D-4 sample to D0 sample for each patient in order to determine which sequence was optimal for administration of B. Routine demographics, toxicity, and engraftment data were also collected.

Results: 41 patients have been enrolled to date, with 34 evaluable for response assessment at day +100. B doses range from 1.0-1.6mg/m² at both time points. Median age is 59 (44-74). Median duration of ANC<500 and pLts <20 was 11 and 5 days respectively, and was not different between the 2 bortezomib sequences. 20 patients have been randomized to ARM A of which 18 are evaluable for response, and 20 to ARM B of which 16 are evaluable for response. 18 of 34 (53%) evaluable patients achieved a VGPR or better at 100 days post transplant, with 32/34 (94%) achieving PR or better. The increase in annexin V and PI staining for the samples obtained from patients who were treated with the ARM B schedule of bortezomib was superior to the increase obtained with ARM A (see figure, p=ns). To date there is no difference in bone marrow IgG or VEGF levels between the arms. There was no difference in mucositis or other toxicity between the 2 treatment arms.

Conclusion: The combination of B and MEL 200 is a safe with engraftment kinetics and toxicity similar to that seen in a historical cohort receiving MEL 200 alone. Efficacy data is favorable when compared to the Mayo clinic retrospective analysis (Kumar BMT 2008) for a group of patients with similar tumor burden at the time of transplant (VGPR 55% current study vs 30% historical). Preliminary lab data suggests that the administration of B following MEL 200 may be superior to B before MEL 200.

Introduction:

Despite numerous advances in oncology, multiple myeloma remains an incurable disease for most patients. Recent advances have included the early use of autologous stem cell transplant for most patients, though this approach is palliative, and nearly all patients will relapse. To date, no conditioning regimen has proven to be more effective than high dose single agent melphalan, which is well tolerated, but ultimately not curative (1). Relapse is thought to occur because of the persistence of resistant disease in the patient, as well as to the re-infusion malignant plasma cells contained within the stem cell graft. Strategies directed at eradication of resistant host cells as well as effective and non-toxic maintenance therapy are clearly needed to address these 2 causes for treatment failure.

Bortezomib has single agent activity in patients with refractory myeloma (2), and is being used earlier in the course of therapy. Studies from Anderson and colleagues (3) at the Dana Farber Cancer Institute as well as from Berenson and colleagues (4) from Cedars Sinai have demonstrated that bortezomib can sensitize previously melphalan-resistant cell lines to melphalan when melphalan and bortezomib are given in combination. Berenson and colleagues have initiated a clinical trial utilizing this preclinical data, and thus far have demonstrated that patients can achieve responses with very low doses of both agents further suggesting the synergistic activity of this combination (5). Anderson and colleagues have also demonstrated, utilizing cultured cells or in vitro models, that timing of the combination between alkylating agents and bortezomib is of critical importance. The synergy of the combination is more pronounced when the alkylating agent is given first followed by bortezomib (6). How this interaction occurs in the context of high dose melphalan, where certain resistance mechanisms can be overwhelmed, is not well understood.

There are limited pre-clinical data on combinations with high dose melphalan primarily because these regimens are difficult to recapitulate in the laboratory models, and often do not effectively model the interactions between human myeloma cells in vivo, the bone marrow stroma, and the post transplant events which govern relapse and treatment related mortality. For this reason, we propose a series of clinical interventions directed at addressing the combination of bortezomib and high dose melphalan as conditioning for autologous stem cell transplant in order to kill more myeloma cells without the burden of added toxicity.

Methods:

Patients who had measurable disease in the bone marrow following induction therapy were considered eligible for the trial. Once eligibility was confirmed, patients were randomized to receive either the A arm (bortezomib before HD MEL 200) or the B arm (bortezomib after HD MEL200).

Bone marrow aspirates were performed before therapy was started (day -4 of transplant) and following completion of conditioning (day 0, or the day of transplant).

Dose escalation was determined using the EWOC method of phase I design (7).

	control	Day+4	Day-3	Day-2	Day-1	Day 0
Melphalan 100mg/m ² (all groups)				X	X	
Bortezomib 1.0, 1.3, or 1.6mg/m ²		A ¹				
Bortezomib 1.0, 1.3, or 1.6mg/m ²					B ²	
Bone Marrow Aspirate			X			X
Stem Cell Infusion						X

RANDOMIZE

EWOC planned Dose escalation

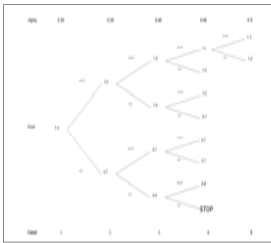
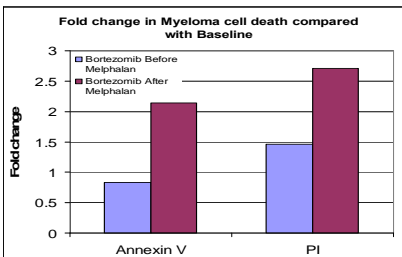
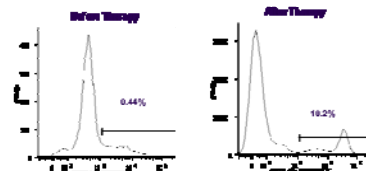


Figure 1. All the possible dose sequences that could be realized for the first four patients and a randomized assignment for patient 5. 5 sequences no simultaneous treatment of patients. The values of alpha used to calculate the next dose is 0.30 for the first patient, increasing by 0.05 at each patient, and stabilizing for patient 5. Alpha is the probability that the dose is allowed the MTD. Low values make the escalation cautious, high values cause aggressive. In the beginning of a trial, there is a higher level of uncertainty about the MTD. Consequently, at the start of a series, the probability of observing a dose higher than the MTD is higher. As the trial progresses, uncertainty about the MTD declines and the likelihood of administering a dose considerably higher than the MTD decreases. Thus, we greatly increased alpha during the course of the trial. When the probability of exceeding the MTD is as low as 0.1, it implies that undergoing a patient (treating with a dose lower than the MTD) is just as bad as overdoing.

Results:

To date 39 patients have been enrolled in this study of which 37 are evaluable, 18 in Arm A (bortezomib before MEL 200) and 19 in Arm B (Bortezomib after MEL 200). Toxicities have been similar between the 2 arms, and there has been no difference in time to neutrophil engraftment (13 days) and platelet engraftment (16 days) compared to historical controls. For response assessment at this time, **Overall response rate is 94% (PR or better) with 19/37 evaluable patients achieving a VGPR or better (56%).**

Myeloma Cell Death in the Marrow before and after Therapy



Results:

Toxicities to date have been predominately transplant related, and are not dissimilar to those from similarly treated patients with MEL 200 alone. Time to neutrophil and platelet recovery are similar to historic data from our center.

1 DLT occurred with the lowest bortezomib dose in Arm B. Additional patients were accrued and no further DLTs were seen. Both arms are now at a bortezomib dose of 1.6mg/m². Based upon the well tolerated experience with this regimen, a second phase I study escalating bortezomib on day +2 is ongoing

Conclusion:

Sequence of administration for the bortezomib /HD MEL 200 combination suggests that the optimal sequence may be bortezomib following MEL 200. This is the adopted sequence for the second dose escalation (all patients receive Bortezomib on day -1 at 1.6mg/m², and second escalation of bortezomib on day +2 (1.0, 1.3, and 1.6 mg/m²)

Novel phase I design allows for safe and rapid dose escalation

Toxicities are similar to previously seen data for MEL 200.

No difference in Toxicity between the 2 randomized arms.

Further toxicity, correlative and response data are ongoing

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