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Phase I trial of bortezomib during maintenance phase after high dose melphalan and autologous stem cell transplantation in patients with multiple myeloma

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Abstract

We enrolled 15 patients in this phase I dose de-escalation trial. Twelve patients are evaluable. The primary objective was to determine the safest and best tolerated maintenance dosing (MD) of bortezomib (B). The secondary endpoints were to evaluate complete response (CR), overall response (OR) and response duration. All patients receiving autologous stem cell transplant (ASCT) were eligible and registered between D + 30 to D + 120 after ASCT. A maximum number of 8 cycles of B was planned. Two evaluable patients in level (L) 1 received therapeutic dose of B 1.3 mg/m² intravenously on days (D) 1, 4, 8, and 11 in a 21 day cycle. Both these patients experienced dose limiting toxicities (DLTs). Four evaluable patients were then enrolled in dose L2 utilizing B 1.3 mg/m² on D 1, 4, 8, and 11 in a 28 day cycle. Two patients in L2 developed DLTs. Six evaluable patients were thereafter enrolled in L3 utilizing B 1 mg/m² on D 1, 8, and 15 in a 28 day cycle. Median 8 cycles of B were administered (2–8). No DLTs were observed in L3. The median duration of follow up for the entire cohort is 33 months (12–62). The median duration of response in L3 is 29.1 months (12–33). We conclude that B 1 mg/m² administered intravenously and may be subcutaneously on D 1, 8, and 15 in a 28 day cycle is the best tolerated MD and can be safely given beginning around D + 100 post-ASCT.

Keywords

Myeloma; Bortezomib maintenance; Autologous stem cell transplantation

Introduction

Multiple myeloma (MM) remains incurable with conventional chemotherapy. Treatment has resulted in improving complete response (CR) rates but enduring remissions remain elusive.^{1,2} High dose chemotherapy with autologous stem cell transplant (ASCT) has resulted in higher CR rates of approximately 50%.³⁻⁵ More intensive therapy, including total therapy 1–3, aimed for a potential cure. However, these treatment regimens did not gain widespread acceptance owing to significant toxicity and higher morbidity.⁶ CR is known to be associated with improved progression free survival (PFS) and overall survival (OS) in MM.⁷⁻¹⁰

Despite achieving CR, all MM patients eventually relapse after high-dose melphalan and ASCT. Novel agents have further improved disease response, and these results are augmented more after ASCT.¹¹⁻¹³ Despite these advances complete disease eradication is not achievable after ASCT. However, to increase the durability of response the concept of maintenance therapy after ASCT has been introduced in this patient population.

Interferon alpha 2b was the first maintenance agent evaluated after induction therapy in MM.¹⁴ It resulted in significantly better response duration (26 vs 14 months), but meta-analysis later demonstrated no significant impact on OS.

Studies have shown the efficacy of oral agents including steroids, thalidomide and lenalidomide post-ASCT resulting in better PFS and possibly OS.¹⁵⁻¹⁹

Bortezomib (Velcade®) despite its efficacy at the approved therapeutic dose in early and relapsed disease stages has not been extensively explored as maintenance therapy, possibly due to intravenous route and twice weekly administration. In a phase 2 study bortezomib (B) 1.3 mg/m² was administered weekly for 4 out of 5 weeks for maintenance therapy (maximum 6 cycles) after ASCT in 40 patients.²⁰ Three-year Kaplan–Meier estimates of disease-free survival and OS were 38.2 and 63.1%, respectively. Neuropathy was observed in 21 (53%) patients and varicella zoster reactivation was observed in 15 (38%) patients. Recently combination therapy with B, thalidomide and dexamethasone induced more CRs when compared to thalidomide and dexamethasone post-ASCT.²¹ Further more consolidation therapy with same agents was also noted to induce prolonged molecular remissions in patients otherwise not considered candidates for allogeneic transplant.²²

Due to lack of data on appropriate B dosing schedule in maintenance phase, we opted for this dose de-escalation design to evaluate the best tolerated maintenance dosing (MD) of B that can be safely administered with minimum side effects in MM patients who have undergone ASCT. B is now approved for subcutaneous administration with similar dose and frequency as intravenous schedule.

Materials and Methods

Patients

This is a phase I dose de-escalation study conducted at Karmanos Cancer Center to determine the safety and tolerability of B in MM patients after high-dose melphalan and ASCT. All patients who received ASCT for MM were eligible for this study. Patients were enrolled between day + 30 to day + 120 after ASCT. Other eligibility criteria included age > 18 years, Karnofsky performance status > 60 and an adequate marrow function defined as absolute neutrophil count > 500/μl and platelets > 75 000/μl.

Patients who were HIV positive, pregnant, and/or had documented resistance or allergy to B were excluded from the study. Those patients with neuropathy > grade 1, concurrent cardiac disease or amyloidosis, bilirubin > 1.5 × ULN, transaminases > 3 × ULN were also excluded from the study. All patients received acyclovir for *varicella zoster virus* prophylaxis during the course of MD.

Study design

This study was designed to be a dose de-escalation trial as the dose in the maintenance setting is predicted to be less than the therapeutic dose for treatment of MM. The primary objective was to determine the safest and best tolerated MD of B.

Secondary end points included the estimation of overall response (OR), CR and the duration of response in patients treated with MD.

In Level (L) 1 the starting dose of B was 1.3 mg/m² administered intravenously on Day 1, 4, 8, and 11 on a 21 day cycle. We planned to enroll three patients initially, and if no toxicity was observed after two cycles, then we would enroll another three patients on this same dose level. If two patients developed dose limiting toxicity (DLT) after two cycles, then further enrollment to that level was stopped. A maximum of eight cycles of treatment were planned. Patients could be maintained on treatment for a maximum of one year from the initiation of the first cycle, or until they had signs of disease progression, death or intolerable side effects that were not resolved with dose adjustment. We initially planned four dose levels, starting at the approved therapeutic dose in L1, and then alternated decreasing dose and increasing interim duration between cycles in other subsequent groups (see Table 1).

Any patient developing grade 4 toxicity by NCI toxicity criteria (v 3.0),²³ would be removed from study. Any patient developing grade 2 toxicity would have therapy stopped until resolution of the toxicity to <grade 1. Subsequent therapy would be administered at 25% (grade 2 toxicity) and 50% dose reductions (grade 3 toxicity).

Response criteria

Disease response was assessed according to SWOG response criteria for MM²⁴ as study was initiated before International Myeloma Working Group uniform criteria was in common use. All baseline evaluations were performed within 30 days of enrollment on the study. Myeloma staging was performed after 4th and 8th cycle, at one year post-initiation of B, progression of disease or at the time of removal from study.

Statistical analysis

Definition of dose limiting toxicity—According to the NCT CTC criteria (v 3.0),²³ any grade 4 thrombocytopenia grade 3 neuropathy, and any other grade 3 toxicity that was directly attributed to B were considered as DLTs. Treatment was discontinued if the toxicity did not resolve in two weeks after discontinuing B and considered DLTs.

The precision of the estimates of OR and CR was estimated with exact binomial 95% confidence intervals. With six patients enrolled at the last dose we had inadequate precision to estimate either OR or CR rate; except if either all or none of the participants responded. Duration of response was described by mean and 95% confidence intervals.

Follow-up—Bortezomib was administered in the outpatient setting. Patients were assessed for clinical and hematological toxicity prior to each dose administration. Myeloma assessment was performed at D + 30 (post-ASCT), after 4th and 8th cycle of maintenance B and at 1 year follow-up visit post-B initiation.

Results

Patient characteristics

We enrolled 15 patients in this study between October 2005 and August 2009. Three patients were not evaluable because two patients withdrew consents and one patient developed persistent thrombocytopenia after signing consent. Median age of the evaluable patients was 59 years (38–68). There were eight males and four females. Median performance status according to Karnofsky Score was 90% (70–100). According to Durie Salmon staging system, eight patients had stage III and four patients had stage II disease. Monoclonal protein sub-type was IgG in five, IgA in five and light chain in two patients.

Baseline grade 1 neuropathy was present in two patients at the time of enrollment. On Fluorescence *in situ* hybridization, nine patients had no cytogenetic abnormalities, one patient had chromosome 13q deletion, one patient had 13 and 17p deletion, and one patient had t(4;14) (Table 2).

Induction regimens comprised immunomodulatory agents and dexamethasone [nine patients (3 thalidomide, 6 lenalidomide)], B and dexamethasone (5 patients) and lenalidomide, B and dexamethasone (1 patient). At the time of transplant, two patients were in unconfirmed complete remission (CRu), three patients had a very good partial response (VGPR), three patients had stable disease (SD), three patients had partial response (PR) and one patient had progression. Single agent high dose melphalan (dose range: 140–260 mg/m²) was administered over 30 minutes on day –2. ASCT was infused on day 0. Median stem cell dose administered was 6.2×10^6 /kg CD34+ cells (range 2.57–24.2) given 48 hours post-melphalan. Median 8 cycles of B were administered (2–8). Bortezomib was started median 103 days post-ASCT (range 47–123).

Toxicity

Two patients were enrolled in L1 on day +52 and day +94 respectively. Both patients developed DLTs and started B < 100 after ASCT. First patient developed grade 3 neuropathy, requiring dose interruption/modification and increasing doses of supportive treatment. Second patient developed grade 3 neutropenia during 2nd cycle which was attributed to B and periodically requiring filgrastim support during remaining cycles. Six patients were then enrolled on L2 and four patients are evaluable. Two patients developed DLTs in L2. First patient started B on day +96 and experienced grade 3 toxicity after 3rd cycle. She experienced fever, hypoxia, severe dehydration, orthostatic hypotension and pulmonary infiltrates resulting hospitalization. She underwent pulmonary evaluation for hypoxia and these symptoms were attributed to B toxicity. Second patient in L2 developed grade 2 neuropathy which did not resolve after two weeks of B interruption, hence categorized as DLTs. Both these patients in L2 who experienced DLT started B < 100 days post ASCT. Subsequent enrollment of seven patients proceeded in L3. DLTs were not observed in any patient in L3.

Maximum eight cycles were administered. In L3 all patients received the planned eight cycles. In L2 only two patients received eight cycles as planned, one patient received three cycles and one patient received two cycles. Both patients with neuropathy at baseline were in L3 and neither of them developed DLTs or worsening neuropathy (Table 3).

Best tolerated maintenance dose of B (MD) after ASCT transplant was determined to be 1 mg/m² administered intravenously on days 1, 8, and 15 in a 28 day cycle. Since no DLTs were noted in L3 this was determined to be best tolerated MD, attaining primary objective of the study. No reactivation of *varicella zoster virus* was observed.

Response

In L1, two patients after ASCT were in CRu and SD respectively. These patients had no prior exposure to B. At the time of development of DLTs they maintained their disease status in CRu and SD respectively. In L2, first patient with SD at the time of enrollment achieved unconfirmed CR after 8 cycles of B and relapsed at 1 year. Second patient was in CR at the time of enrollment and remained in unconfirmed CR at the time of DLTs after three cycles. Third patient was in PR initially and had PR as best response at one year. Fourth patient had PR at the time of enrollment and had no evidence of progressive disease at the time of DLT. In L3, 3 patients had VGPR, one patient each had PR, SD and relapse at the time of enrollment. First patient with relapse disease at baseline achieved unconfirmed

CR after 4 cycles but then had evidence of relapse after 8 cycles. Second patient in VGPR converted to unconfirmed CR after 8 cycles but then had relapse disease at one year follow-up. Third patient in VGPR had progressive disease after 8 cycles. Fourth patient had PR at enrollment and had stable disease after 8 cycles and at one year. Fifth patient maintained SD throughout after enrollment. Sixth patient was in VGPR upfront and had SD after 8 cycles and at one year (Table 3).

Assessment of response

Nine patients (75%) either maintained or had improvement in disease response at the time of assessment performed after completion of 8 cycles of B. Fifty per cent (3/6) of patients in L3 had evidence of disease relapse/progression after 8 cycles of therapy.

Discussion

Maintenance therapy with novel agents after ASCT is gaining acceptance as it improves duration and depth of response. There is evolving evidence that it may also improve OS.^{16,25} Novel agents that are widely available have been utilized for maintenance therapy after ASCT. Administering prolong sub-therapeutic maintenance therapy raises a concern for selection of more resistant cells by virtue of constant exposure of these cells to one of the most active agents. This observation has been made in the past with the use of thalidomide as maintenance therapy after ASCT.¹⁷

Thalidomide maintenance has been attempted in six randomized studies.^{16-18,26-28} Thalidomide improves EFS and PFS but OS benefit was only evident in three trials.^{16,25,27} One of these trials was later retracted.²⁹ Differences in trial design, MD and duration of thalidomide makes the interpretation of these results very difficult. Despite these promising results thalidomide maintenance therapy has not gained wider acceptance owing to concerns about its side effect profile of neurotoxicity, which is dose related. In most of these studies the incidence of grade 3–4 peripheral neuropathy was in the range of 7–27% and was the predominant reason for stopping maintenance therapy.

Lenalidomide as maintenance therapy appeared to be the next logical step since it is devoid of neurological toxicity. Attal *et al.*³⁰ evaluated lenalidomide for maintenance therapy after ASCT. PFS improved from 35% in the placebo arm to 68% in lenalidomide arm (P 10⁻⁶). McCarthy *et al.*³¹ also studied the use of lenalidomide after ASCT. After a median follow-up of 12 months the median time to progression has not been reached in lenalidomide arm. However, long-term side effects of lenalidomide therapy are not known. Lenalidomide maintenance therapy was evaluated in another phase 2 study utilizing B induction therapy followed by ASCT. After median follow-up of 21 months, the 2-year PFS was 69%, and OS was 86%.¹⁹ However, the role of lenalidomide as maintenance therapy is still under further investigation.

However, the dosages and duration of novel drugs utilized for maintenance have not been formally determined in a phase I dose escalation trial. The maintenance dose selected for all the novel agents in majority of these studies is less than the therapeutic dose. These agents though beneficial have their respective side effects. One of the aims behind ASCT is to provide freedom from continuous therapy and associated side effects for a prolonged period, in order to improve the quality of life. Unfortunately relapse is universal, and majority of patients have persistent disease after ASCT. All patients in our study received single ASCT. Tandem transplant in North America is not performed routinely regardless of disease status after first ASCT. Therefore evaluating the maintenance dose of these novel agents after ASCT seems rational and very important.

Preliminary results of randomized trials using B in consolidation and maintenance setting after ASCT are encouraging.^{21,22,32} To our knowledge this is the first phase I study evaluating the MD of B after ASCT. It is important to note that all patients who experienced DLTs in L1 and L2 started B < 100 days after ASCT. We determined that the B dose used in L3 1 mg/m² administered on D 1, 8, 15 every 28 days cycle is the best tolerated MD. Patients at this dose level did not experience any DLTs during the study. The numbers of patients in this level are inadequate to determine the response from therapy given the phase I design of the study. However, we observed that nine patients (75%) had no evidence of progression/relapse while they were on maintenance B. The primary objective of an ideal maintenance drug is to prolong PFS and OS with minimal toxicity. The response to B maintenance was seen irrespective of its use in induction therapy prior to ASCT. Furthermore, patients who received immunomodulatory agents as part of induction therapy also had some responses (Table 4). Number of cycles in our study was restricted to eight, matching the current therapeutic recommendations. The maintenance therapy was not continued until progression even in responding patients, so we are unable to comment on the side-effects of B on prolonged exposure. Neuropathy in our study was assessed clinically, and was not documented more rigorously according to recently published guidelines.³³ However, the once weekly schedule has been known to have lesser neurological toxicity.³⁴

Accrual in this study was slow due to insurance issues and logistics of B administration. The total number of cycles was therefore limited to 8. Ultimately the optimal duration of B maintenance remains to be determined from future studies. It is reasonable to continue maintenance therapy until progression or development of toxicity. Further improvement in study design could also be instituted by addition of criteria such as performance status and presence of baseline neuropathy. Recently, B is administered subcutaneously for relapsed myeloma and this might be a better alternate route for prolonged maintenance drug administration.³⁵ We further recommend studying the role of B maintenance therapy after ASCT in low and high risk patients to maintain response. The addition of steroids in maintenance therapy combined with B post-ASCT is another potential combination that might be evaluated especially in patients with poor performance status and not eligible for ASCT as evaluated by our Spanish colleagues in non-transplant setting.³⁶

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Table 1

Schema

Dose Determination Schedule	
Dose Level	Dose of Bortezomib*
Level 1	1.3 mg/m ² I.V on Day 1, 4, 8, 11 – Every 21 days
Level 2	1.3 mg/m ² I.V on Day 1, 4, 8, 11 – Every 28 days
Level 3	1.0 mg/m ² I.V on Day 1, 8, 15 – Every 28 days
Level 4	1.0 mg/m ² I.V on Day 1, 8, 15 – Every 35 days

* Doses are stated as exact dose in units (mg/m²)

I.V: Intravenous.

Table 2Patient characteristics at baseline (*n*=12)

Variables	Patients <i>N</i>
Age (years), median (range)	59 (38–68)
Gender	
Male	8
Female	4
Race	
Caucasians	10
African Americans	1
Others	1
Durie Salmon Staging	
Stage II	4
Stage III	8
Cytogenetics	
Standard risk	9
High risk *	3
Paraprotein isotype	
IgG	5
IgA	5
Light chains	2
Disease status at ASCT	
CRu	2
VGPR	3
PR	3
SD	3
Relapse	1
Maintenance initiation (day post-ASCT)	
Median (range)	100 (47–123)

Note:

* High risk: t(4:14); Chromosome 13 del, del 17p.

Cru, unconfirmed complete response; VGPR, very good partial response; PR, partial response; SD, stable disease.

Table 3

Dose limiting toxicities (DLTs) according to dose level assignment

Dose level	Co-morbidities	Day post-ASCT* maintenance started	DLT
L1	Type 2 Diabetes	52	Grade 3 – sensory neuropathy
		94	Grade 3 – neutropenia
L2		96	Grade 3 – hospitalized for severe dehydration, fever, nausea and pulmonary toxicity
		82	Grade 2 – sensory neuropathy that did not resolve within 2 weeks after stopping B
			Grade 3 – moderate to severe fatigue

Note:

* Day 0: ASCT infusion.

Table 4

Response

Dose level	Pt. no.	Induction regimen	Status at ASCT	Status after completion of bortezomib	Status at 1 year post-starting bortezomib
L1	1	Thalidomide, Dexamethasone	CRu	CRu*	
	2	Thalidomide, Dexamethasone	SD	SD*	
L2	1	VAD, Bortezomib, Thalidomide	SD	CRu	Relapse
	2	Lenalidomide, Dexamethasone	CRu	CRu*	
	3	VAD, Melphalan, Bortezomib	PR	PR	PR
	4	Lenalidomide, Dexamethasone	PR	SD*	
L3	1	VAD, Bortezomib,	Relapse	PD	PD
	2	Lenalidomide, Bortezomib	VGPR	CRu	Relapse
	3	Bortezomib, Liposomal Doxorubicin, Dexamethasone	VGPR	PD	PD
	4	Lenalidomide, Dexamethasone	PR	PD	SD
	5	Lenalidomide, Dexamethasone	SD	SD	SD
	6	Lenalidomide, Bortezomib, Dexamethasone	VGPR	SD	SD

Note: ASCT, autologous stem cell transplant; CRu, unconfirmed CR (no bone marrow biopsy performed); VAD, vincristine, adriamycin, dexamethasone.

* patient developing DLT.