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ARTICLE

A phase I/II study of escalating doses of thalidomide in conjunction with bortezomib and high-dose melphalan as a conditioning regimen for autologous stem cell transplantation in patients with multiple myeloma

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Abstract

A regimen of escalating doses of thalidomide, in combination with bortezomib and high-dose melphalan (mel/vel/thal), was evaluated as a conditioning regimen for autologous stem cell transplantation (ASCT) in multiple myeloma (MM) patients with a prior transplant who had relapsed or achieved less than a complete remission following a prior ASCT. Thalidomide was dose escalated starting from 600 mg to 1000 mg on days −5 to −1 in a 3 × 3 design, bortezomib was administered at 1.6 mg/m^2 intravenously on days −4 and −1 and melphalan 200 mg/m^2 was administered on day −2. No dose-limiting toxicity was seen in the phase I portion of the trial. An additional 20 patients were enrolled at the maximum tolerated dose of thalidomide of 1000 mg daily. The overall response rate was 69% with 38% complete remission. Median PFS and OS were 9.3 and 65.4 months, respectively, with a median follow-up of 17.8 months. The most common grade 3–4 adverse events (AEs) were neutropenic fever (58.6%), mucositis (6.9%), and diarrhea (6.9%). Serious AEs included somnolence (13.8%) and tumor lysis syndrome (3.4%). The addition of high-dose thalidomide to bortezomib and melphalan as conditioning for salvage ASCT was well tolerated and was an effective conditioning regimen.

Introduction

Therapy for multiple myeloma (MM) has markedly changed in the past decade with the introduction of proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs), improving survival for patients from a 5-year overall survival (OS) of 31% a decade ago to 49.6% [1, 2]. Despite the treatment advances, MM continues to be considered incurable with standard therapy. Randomized studies demonstrated a superior progression-free survival (PFS) and some demonstrated an improved OS in newly diagnosed MM patients who received upfront autologous stem cell transplantation (ASCT) compared to conventional chemotherapy [3–5]. Older studies of dose-intense melphalan followed by single or tandem ASCT were shown in randomized studies to be effective in achieving remissions of 2.5–3.5 years [6–9]. Recent incorporation of maintenance lenalidomide has further improved PFS beyond 3.5 years [10, 11]. In the relapsed or salvage setting, for patients who achieved durable remissions from their first melphalan-based ASCT, an additional cycle of dose-intense melphalan followed by ASCT achieved favorable outcomes, with a median PFS of 8.5–17.3 (proportional to the duration of the response to the prior cycle of dose-intense therapy) months as demonstrated in single site studies and registry (Center for International Blood and Marrow Transplant Research; CIBMTR) analysis [12–15]. Thus, a salvage transplant is a consideration for relapsed patients after a prolonged event-free interval after a preceding autologous transplant.

Single-agent melphalan 200 mg/m^2 is the worldwide standard conditioning regimen for ASCT in MM. To date,

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	Day of transplant						
		–5	–4	–3	–2	–1	Transplant day
Thalidomide		X	X	X	X	X	
Bortezomib			X			X	
Melphalan					X		
PBSC infusion							X

Fig. 1 Treatment schema for conditioning regimen. The above illustrates the dosing schedule and frequency of the melphalan, bortezomib, and thalidomide conditioning regimen

most modifications of the ASCT conditioning regimens have not been able to improve the median PFS or OS [16].

We recently evaluated escalating doses of the proteasome inhibitor bortezomib in conjunction with high-dose melphalan as a conditioning regimen for salvage ASCT in 32 patients with relapsed or refractory MM after initial ASCT in a phase I/II study. We observed 2-year PFS and OS probabilities of 76% and 39%, respectively [17]. No overlapping toxicities were demonstrated. Thalidomide, an immunomodulatory agent, in combination with melphalan and bortezomib has been well described in nontransplant settings [18–20]. The aim of this study is to investigate the safety and efficacy of the coadministration of bortezomib, dose-intense melphalan and thalidomide as a conditioning regimen for ASCT in MM.

Materials and methods

Patient enrollment

Patients were enrolled between June 2010 and August 2012 (Clinical trial ID NCT01242267). Patient eligibility criteria included two groups of patients: (1) Upfront tandem ASCT: patients with a confirmed diagnosis of MM with less than a complete response to a prior cycle of dose-intense melphalan measured at 8 weeks after ASCT and (2) Salvage ASCT: patients with progression of disease after a previous ASCT ("relapsed"). Additional inclusion criteria included: age >18 and <76 years and the availability of autologous peripheral blood stem cell products containing at least 2×10^6 CD34+ cells/kg. Relapsed patients may have received intervening therapies in the management of progressive MM. Exclusion criteria included chemotherapy or radiation therapy within 28 days of initiating treatment in this study, prior ASCT within 56 days, uncontrolled infections, CNS metastasis, known cardiac amyloid, serious organ dysfunction, or grade 4 peripheral neuropathy. Although nonsecretory disease was not part of the exclusion criteria, all enrolled subjects had measurable disease. Informed consent was obtained prior to enrollment for all patients, using consent forms approved by the IRB of Hackensack University Medical Center. High-risk cytogenetics was defined per the International Myeloma Working Group [21].

Treatment schema

The treatment schema is shown in Fig. 1. All patients received melphalan 200 mg/m^2 intravenously over 60 min based on actual body weight on day −2 before ASCT (day 0). Bortezomib 1.6 mg/m^2 was given i.v. by rapid infusion (over 3–5 s) on days −4 and −1 (of note, this study was completed prior to the approval of subcutaneous bortezomib). Thalidomide was administered on days −5 to −1 at the dose-escalating schedule as detailed below. Dexamethasone (as an anti-emetic), 20 mg i.v., was given in conjunction with each bortezomib injection and on days of thalidomide for those patients who received the 1000 mg dose (to counteract the sedative effects of thalidomide) and 10 mg i.v. on day −2 in prior to melphalan. Day 0 was defined as the first day of stem cell infusion. All patients received standard supportive care regimens including antiemetics, prophylactic antibiotics, and blood component support. Granulocyte-colony stimulating factor, 5 mcg/kg, was administered by subcutaneous injection on alternate days starting on day +3, and daily starting on day +9, until an absolute neutrophil count of $\geq 0.5 \times 10^9$/l was achieved.

For the phase 1 portion, patients were admitted to the hospital and thalidomide was administered at a starting dose of 600 mg orally per day, with subsequent cohorts of patients treated with 800 and 1000 mg given daily. Cohorts of three patients were to be enrolled at each dose level. An additional three patients were added if one of three patients suffered a nonhematological severe adverse effect (SAE) of greater than 3 based on Common Toxicity Criteria v 3.0 toxicity grading scales [22]. Dose-limiting toxicity (DLT) was defined as two nonhematological SAEs occurring at a dose level, and no further dose-escalation was to be allowed. The maximum tolerated dose (MTD) was defined as the dose level less than the one at which the DLT occurred. An additional 20 patients were enrolled at the MTD in the phase II portion of this study.

It is important to note that none of the patients received lenalidomide or any other maintenance/consolidation therapy after their mel/vel/thal ASCT.

Evaluation criteria

Response and relapse followed the International Myeloma Working Group uniform response criteria [23] with the following modification: because the study did not mandate bone marrow evaluation to confirm a complete response, a category of immunofixation-negative CR, or biochemical CR, was defined as confirmed disappearance of the monoclonal protein in the serum and urine by immunofixation studies without the requirement for bone marrow studies. Responses were compared relative to the last line of therapy. Patients were seen daily after transplant and monitored for toxicities until engraftment. Responses were evaluated at +28, +56 and +84 days after transplantation and then every 3 months thereafter.

Statistical analysis

The primary objective of the study was to determine the maximum tolerated dose of thalidomide used in conjunction with melphalan (200 mg/m^2) and bortezomib with ASCT. Secondary objectives included determination of overall response rate (ORR) PFS and OS.

Descriptive statistics (median and range for continuous variables; count and percentage for categorical variables) are used to summarize patients' characteristics. Survival distributions were estimated using the Kaplan−Meier (KM) method. PFS was defined as the time from ASCT to disease progression or death from any cause. Patients were also censored for PFS at the time of alternative therapy such as allogeneic stem cell transplantation. OS was defined as the time from ASCT to death, with patients censored at time of initiation of allogeneic or third autologous stem cell transplant, if given.

Results

Twenty-nine patients with MM were enrolled in the trial. The phase I portion consisted of nine patients, with three patients enrolled at each dose level 600, 800, and 1000 mg. No DLTs were observed at any level. An additional 20 patients were enrolled in the phase II portion at the 1000 mg dose level. Patient baseline characteristics are provided in Table 1: Forty-eight percent were of male sex with a median age at transplantation of 56 years (range 40–70). Patients were mostly IgG isotype (75.9%) and Durie-Salmon stage III (93%). Cytogenetic and/or fluorescent in situ hybridization (FISH) analysis was available for 58% of patients, of which most were standard risk. Of patients for whom cytogenetic data were available, five patients (17.2%) had high-risk disease including two with del 17p, one with t (4;14), and four (14%) with del 13q by cytogenetics. Eighty-six percent had a prior proteasome inhibitor (PI), 86% had a prior immunomodulatory agent (IMiD), 79% had prior PI and IMiD, 37.9% were IMiD-refractory, and 37.9% were PI-refractory at the time of their mel/vel/thal ASCT.

All patients received one previous ASCT prior to enrolling on the study. Seventeen (59%) of the 29 patients received the mel/vel/thal as a salvage transplant. All of these patients had interim salvage chemotherapy between their first ASCT and mel/vel/thal ASCT. The median number of prior lines in this group was 3 (range 1–7). Twelve of the 17 (71%) salvage patients had three or more prior lines of therapy. Of the 17 patients in the salvage group, 86% had prior lenalidomide, 36% had thalidomide, 100% had bortezomib and 14% had carfilzomib. Immediately prior to salvage ASCT, 6/17 (35%) were on an IMiD and proteasome inhibitor (PI)-based triplet, 3/17 (17.6%) were on a PI/alkylating agent-based triplet, 4/17 (23.5%) were on an IMiD or PI-based doublet, 2/17 (12%) were on a PI and IMiD-based quadruplet, and 2/17 (12%) were on vorinostat + lenalidomide. Disease status immediately prior to mel/vel/thal ASCT included 11/17 (64.7%) disease progression 4/17 (23.5%) partial remission, 2/17 (11.8%) ≥ VGPR. For the salvage ASCT cohort, the median time to progression of disease after the first transplant was 11.9 months and the median time from the first to the salvage transplant was 29 months.

Twelve (41%) of the 29 patients who had achieved less than a CR at 8 weeks with an upfront transplant received a mel/vel/thal ASCT (i.e. received an "unplanned" tandem transplants). Median time from first to second ASCT was 6.2 months. Four (13.7%) patients who underwent subsequent allogeneic stem cell transplant are not evaluable for long-term response.

Outcomes from the mel/vel/thal ASCT are reported in Table 2. The median peripheral stem cell dose was 6.42 × 10^6 (range, 4–13.06) CD34+ cells/kg. All patients achieved neutrophil engraftment at a median of 10 days (range, 9–14 days) and platelet engraftment at a median of 12 days (range, 9–26 days). The median duration of hospitalization was 16 (range, 11–24) days.

Response evaluation

Best response following ASCT is summarized in Table 2. The ORR was 69%: 11 patients (38%) achieved a biochemical CR, 6 (21%) achieved a VGPR, 3 (10%) achieved PR, 5 (17%) had stable disease (SD), and 1 (3.4%) was nonevaluable. Of the 11 patients who achieved a CR, 5

Table 1 Baseline characteristics

Characteristic	Overall ($N = 29$)	Phase I ($N = 9$)	Phase II ($N = 20$)
Sex, *N* (%)			
Male	14 (48.3)	3 (33.3)	11 (55)
Age, median (range)			
at diagnosis	52 (38–69)	58 (42–69)	51 (38–65)
at mel/vel/thal ASCT	56 (40–70)	59 (50–70)	55 (40–70)
Salvage ASCT	17 (58.6)	6 (66.7)	11 (55)
Tandem ASCT	12 (41.3)	3 (33.3)	9 (45)
Subclass, *N* (%)			
IgG	22 (75.9)	7 (77.8)	15 (75)
IgA	3 (15.6)	0	3 (15)
FLC	2 (6.9)	1 (11.1)	1 (5)
Nonsecretory	2 (6.9)	1 (11.1)	1 (5)
Plasma cell leukemia	2 (6.9)	1 (11.1)	1 (5)
Durie Salmon Stage, *N* (%)			
I	1 (3.4)	1 (11.1)	0
II	1 (3.4)	1 (11.1)	0
III	27 (93.1)	7 (77.8)	20 (100)
FISH/cytogenetic abnormality, *N* (%)			
High			
Del 17p	2 (6.9)	1 (11.1)	1 (5)
Intermediate			
t(4;14)	1 (3.4)	0	1 (5)
Del 13 or monosomy 13 (cytogenetics)	4 (13.8)	2 (22.2)	2 (10)
Standard			
t(11;14)	2 (6.9)	0	2 (10)
Other standard risk	9 (31.0)	5 (55.6)	4 (20)
Unknown	12 (41.4)	2 (22.2)	10 (50)
No. prior transplants, *N* (%)			
1	28 (96.6)	8 (88.9)	20 (100%)
2	1 (3.4)	1 (11.1)	0
No. lines prior to first transplant, *N* (%)			
0	1 (3.4)	0	1 (5)
1	18 (62.1)	5 (55.6)	13 (65)
2	8 (27.6)	3 (33.3)	5 (25)
≥3	2 (6.9)	1 (11.1)	1 (5)
Prior regimens			
PI exposed	25 (86)	7 (77.8)	18 (90)
IMiD exposed	25 (86)	8 (88.9)	17 (85)
IMiD and PI exposed	23 (79)	7 (77.8)	16 (80)
IMiD refractory	11 (37.9)	4 (44.4)	7 (35)
PI refractory	11 (37.9)	2 (22.2)	9 (45)
Response status after first transplant, *N* (%)			
Complete remission	4 (13.8)	1 (11.1)	3 (15)
Very good partial remission	7 (24.1)	1 (11.1)	6 (30)
Partial remission	7 (24.1)	4 (44.4)	3 (15)
Stable disease	7 (24.1)	2 (22.2)	5 (25)
Disease progression	0	0	0
Unable to determine	3 (10.3)	0	3 (15)
Salvage ASCT	17 (58.6)	6 (66.7)	11 (55)
Tandem ASCT	12 (41.3)	3 (33.3)	9 (45)
No. lines between first ASCT and mel/vel/thal ASCT, *N* (%)			
0	15 (51.7)	5 (55.6)	10 (50)
1	4 (13.8)	0	4 (20)
2	6 (20.7)	4 (44.4)	2 (10)
≥3	4 (13.8)	0	4 (20)

ASCT autologous stem cell transplantation, *PI* proteasome inhibitor, *IMiD*immunomodulatory agent, *FISH* fluorescent in situ hybridization

Table 2 Outcomes with melphalan-bortezomib-thalidomide autologous stem cell transplant

Characteristic	Overall ($N = 29$)	Phase I ($N = 9$)	Phase II ($N = 20$)
Thalidomide dose, *N* (%)			
600 mg	3 (10.3)	3 (33.3)	0
800 mg	3 (10.3)	3 (33.3)	0
1000 mg	23 (79.3)	3 (33.3)	20 (100)
Bortezomib dose, *N* (%)			
1.6 mg/m^2	29 (100)	9 (100)	20 (100)
Melphalan dose, *N* (%)			
200 mg/m^2	29 (100)	9 (100)	20 (100)
Cell dose $\times 10^6$ CD34+ cells/kg, median (range)	6.42 (4–13.06)	7.85 (5.67–13.06)	6 (4–8.53)
Engraftment kinetics days, median (range)			
ANC $\geq 0.5 \times 10^9$/l	10 (9–14)	10 (9–10)	10 (9–14)
Platelets $\geq 20 \times 10^9$/l	12 (9–26)	12 (9–15)	13 (9–26)
Duration of hospitalization, median (range)	16 (0–29)	14 (0–24)	16 (15–29)
Best response, *N* (%)			
CR	11 (37.9)	4 (44.4)	7 (35)
VGPR	6 (20.7)	0	6 (30)
PR	3 (10.3)	1 (11.1)	2 (10)
SD	5 (17.2)	2 (22.2)	3 (15)
PD	3 (10.3)	2 (22.2)	1 (5)
Not evaluable	1 (3.4)	0	1 (5)
ORR	20 (69.0)	5 (55.6)	15 (75)

CR complete remission, *VGPR* very good partial remission, *PR* partial remission, *MR* minor remission, *SD* stable disease, *PD* disease progression, *ORR* overall response rate defined as CR + VGPR + PR

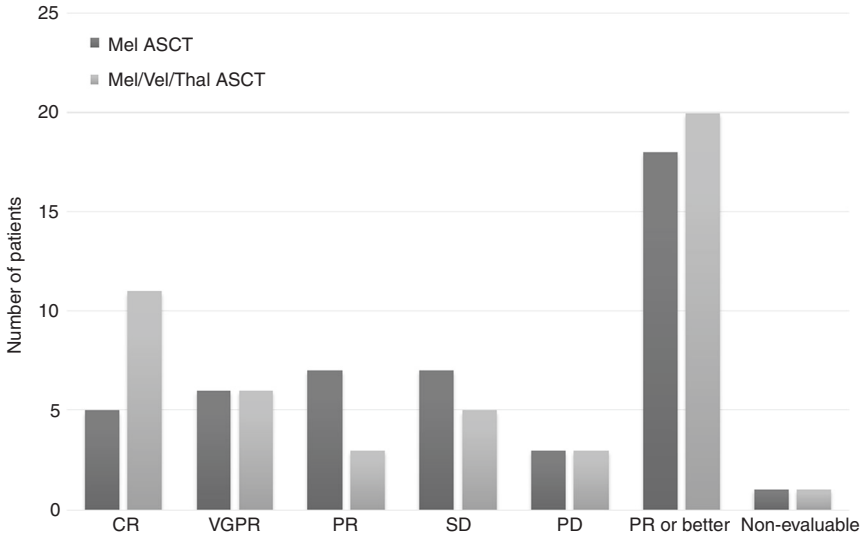

Fig. 2 Best response with first mel-ASCT compared to mel-vel-thal-ASCT. CR complete remission, VGPR very good partial remission, PR partial remission, SD stable disease, PD progressive disease, ASCT autologous stem cell transplantation

received a tandem mel/vel/thal ASCT and 6 received a salvage mel/vel/thal ASCT. Response after the first melphalan ASCT was compared to response after mel/vel/thal ASCT and is demonstrated in Fig. 2. Eleven patients achieved a biochemical CR with mel/vel/thal compared to 5 patients with melphalan alone, and 20 patients achieved a ≥PR with mel/vel/thal compared to 18 patients with melphalan alone. Ten of 27 evaluable patients (37%) had an upgrade in response in the mel/vel/thal salvage ASCT compared to their upfront ASCT: 2 pts (7%) went from PD to PR, 1 (4%) from SD to CR, 1 (4%) from PR to VGPR; 3 (11%) from PR to CR and 2 (7%) from VGPR to CR.

Survival probabilities

With a median follow-up of 17.8 months, the median PFS and OS were 9.3 and 65.4 months, respectively, for the entire cohort (Fig. 3a). The median PFS and OS for patients who received mel/vel/thal as a tandem ASCT was 14.9 months and not reached, respectively. In patients who received mel/vel/thal as a salvage transplant, the median PFS and OS were 9.1 and 17.8 months, respectively (Fig. 3b).

Toxicities

Nonhematological toxicities were graded based on the CTCAE v3.0 Criteria and are summarized in Table 3. Toxicities of grade 3 and above were considered significant. In the phase 1 portion, all patients experienced somnolence, with grade 3 occurring in one patient at the 800 mg/day dose. Subsequently, dex 40 mg was given with the first dose of thal at the 1000 mg level with decreased severity of somnolence. There were no unexpected hematologic toxicities. The most common grade 1–2 toxicities included nausea, (65.5%), mucositis (51.7%), diarrhea (48.3%), somnolence (48.3%), lethargy (27.6%), vomiting (17.2%), dysgeusia (13.8%), and anorexia (13.8%). The most common nonhematological grade 3 toxicities included neutropenic fever (58.6 with 41.4% culture-negative) and mucositis (6.9%). There were three SAEs. One patient experienced grade 3 lethargy and somnolence characterized by episodes of perseveration, confusion, horizontal nystagmus and multifocal myoclonus, all of which resolved with supportive care. Another patient developed renal failure as a result of tumor lysis syndrome. A third patient was re-admitted 20 days after mel/vel/thal ASCT for management of a flare of rheumatoid arthritis requiring intravenous corticosteroids. There was no acute emergent neuropathy nor increase in pre-existing neuropathy. There were no deaths or ICU admissions on study. A secondary primary malignancy, multiple squamous cell carcinomas of the skin, was observed in one patient.

Discussion

Although the combination of high-dose melphalan with bortezomib and thalidomide has been retrospectively described in MM patients receiving upfront and salvage single or tandem ASCT [20], this is the first study to prospectively evaluate the combination of melphalan 200 mg/m^2 given as a single dose in combination with bortezomib and thalidomide. It has been well documented that high-dose therapy with ASCT improves PFS, and, in some studies OS, following initial induction therapy, as upfront tandem [24–26], and in the salvage setting [12–14, 27–31] compared to nontransplant containing therapies. Regarding salvage ASCT, the American Society of Blood and Marrow Transplant, European Society of

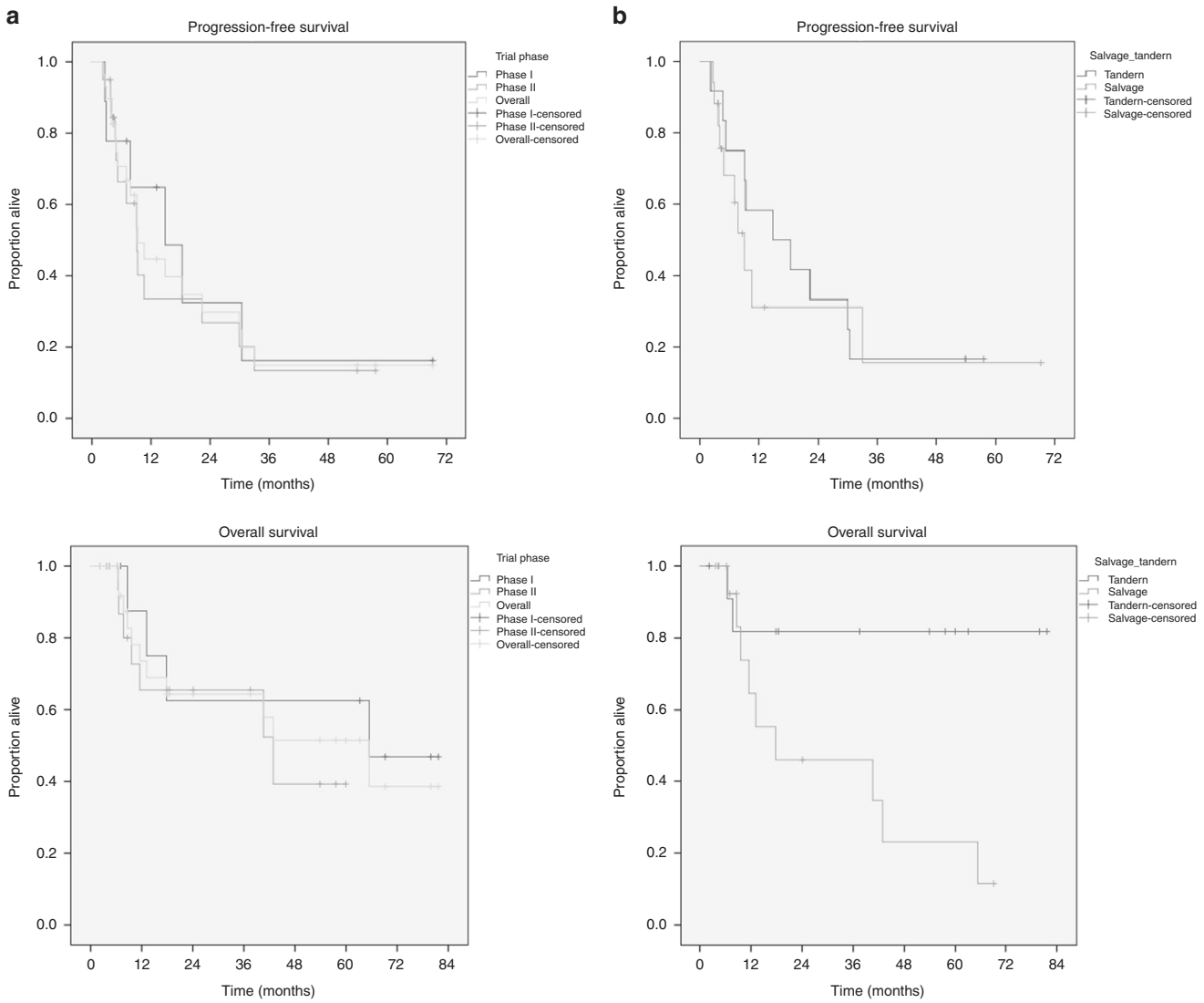

Fig. 3 Progression-free and overall survival. **a** Progression-free survival and overall survival among all patients by phase of study. **b** Progression-free survival and overall survival by tandem vs. salvage mel/vel/thal ASCT. ASCT autologous stem cell transplantation

Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network and International Myeloma Working Group have published guidelines recommending consideration of ASCT for patients relapsing after primary therapy without a prior ASCT and for those patients whose remission duration exceeded 18 months after a prior ASCT [32].

Although primary resistance to high-dose melphalan is rare, there is a subset of patients who are resistant to high-dose melphalan or who do not achieve a durable remission [33, 34]. Thus, combination regimens have the potential to overcome resistance. Other studies have looked at various combination conditioning regimens for ASCT including carfilzomib plus melphalan [35] and busulfan, bortezomib, and melphalan [36]. Although these combinations appear promising in terms of ORR and PFS, follow-up data are limited.

Several studies have shown that the proteasome inhibitor bortezomib is an excellent candidate for combination therapy with high-dose melphalan. In the ASCT setting, bortezomib has been combined with dose-intense melphalan. A phase II study carried out by Roussel et al. demonstrated a 32% complete remission (CR) in patients receiving bortezomib and melphalan as conditioning regimens prior to upfront ASCT. The PFS at 2 years was 88% [37]. In a phase I/II study conducted by our group, escalating doses of bortezomib with high-dose melphalan was evaluated in 22 patients with MM who achieved less than a partial remission compared to their pretransplant paraprotein after a prior ASCT [17], in both the tandem and salvage settings.

Table 3 Toxicities with mel/vel/thal ASCT

	All patients ($N = 29$)	Phase I ($N = 9$)	Phase II ($N = 20$)
Nonhematologic toxicities			
Cardiovascular			
Hypotension			
Grade 3	1 (3.4)	1 (11.1)	0
Hypertension			
Grade 3	1 (3.4)	0	1 (5)
Pulmonary hypertension			
Grade 1/2	1 (3.4)	0	1 (5)
Mild left atrial dilatation			
Grade 1/2	1 (3.4)	0	1 (5)
Bradycardia			
Grade 1/2	2 (6.9)	1 (5)	1 (5)
Deep venous thrombosis			
Grade 3	2 (6.9)	0	2 (10)
Gastrointestinal			
Nausea			
Grade 1/2	19 (65.5)	7 (77.8)	12 (60)
Grade 3/4	1 (3.4)	0	1 (5)
Diarrhea			
Grade 1/2	14 (48.3)	6 (66.7)	8 (40)
Grade 3/4	2 (6.9)	0	2 (10)
Vomiting			
Grade 1/2	5 (17.2)	2 (22.2)	3 (15)
Anorexia			
Grade 1/2	4 (13.8)	0	4 (20)
Mucositis			
Grade 1/2	15 (51.7)	4 (44.4)	11 (55)
Grade 3/4	2 (6.9)	0	2 (10)
Acid reflux			
Grade 1/2	1 (3.4)	0	1(5)
Dry mouth			
Grade 1/2	1 (3.4)	0	1(5)
Constipation			
Grade 1/2	1 (3.4)	0	1(5)
Abdominal pain/ cramping			
Grade 1/2	2 (6.9)	1 (5)	1 (5)
Odynophagia			
Grade 1/2	3 (10.3)	0	3 (15)
Dysgeusia			
Grade 1/2	4 (13.8)	2 (22.2)	2 (10)
Constitutional/Neurologic			
Somnolence			
Grade 1/2	14 (48.3)	8 (88.9)	6 (30)
Grade 3	1 (3.4)	0	1 (5)
Neuropathy			
Grade 1/2	5 (17.2)	1 (11.1)	4 (20)
Fatigue			
Grade 1/2	7 (24.1)	2 (22.2)	5 (25)
Dizziness			
3 (10.3)	1 (11.1)	2 (10)	
Failure to thrive			
Grade 1/2	1 (3.4)	1 (11.1)	0
Headache			
Grade 1/2	1 (3.4)	1 (11.1)	0
Renal/Electrolytes			
Renal impairment			
Grade 1/2	2 (6.9)	1 (11.1)	1 (5)
Grade 3/4	1 (3.4)	0	1 (5)
Fluid overload			
Grade 1/2	1 (3.4)	0	1 (5)
Dehydration			
Grade 1/2	1 (3.4)	1 (11.1)	0
Urinary hesitancy			
Grade 1/2	1 (3.4)	0	1 (5)
Prostatism			
Grade 1/2	1 (3.4)	0	1 (5)
Tumor lysis syndrome			
Grade 3/4	1 (3.4)	0	1 (5)
Infectious			
Fever			
Grade 2	1 (3.4)	0	1 (5)
Febrile neutropenia			
Grade 3	17 (58.6)	4 (44.4)	13 (65)
Febrile neutropenia (culture-negative)			
Grade 3	12 (41.4)	1 (11.1)	11 (55)
Pulmonary			
Bronchospasm			
Grade 1/2	1 (3.4)	0	1 (5)
Dyspnea			
Grade 3	2 (6.8)	0	2 (10)
URI			
Grade 1/2	1 (3.4)	0	1 (5)
Cough			
Grade 1/2	1 (3.4)	0	1 (5)
Dermatologic and musculoskeletal			
Joint pain			
Grade 1/2	1 (3.4)	0	1 (5)
Joint effusion			
Grade 3	1 (3.1)	0	1 (5)
Weakness low extremity/ generalized			
Grade 1/2	8 (27.6)	1 (11.1)	7 (35)
Low extremity pain/ cramping			
Grade 1/2	2 (6.8)	1 (11.1)	1 (5)
Low extremity edema			
Grade 1/2	3 (10.3)	0	3 (15)
Soft tissue mass of the hand			

Table 3 (continued)

	All patients ($N = 29$)	Phase I ($N = 9$)	Phase II ($N = 20$)
Grade 1/2	1 (3.1)	0	1 (5)
Sexual/reproductive			
Breast discomfort			
Grade 1/2	1 (3.1)	0	1 (5)
	All patients ($N = 29$)	**Phase I ($N = 9$)**	**Phase II ($N = 20$)**
Nonhematologic toxicities			
Nausea	20 (69.0)	7 (77.8)	13 (65)
Vomiting	5 (17.2)	2 (22.2)	3 (15)
Diarrhea	16 (55.2)	6 (66.7)	10 (50)
Mucositis	17 (58.6)	4 (44.4)	13 (65)
Neuropathy	5 (17.2)	1 (11.1)	4 (20)
Infection sources			
Gram-positive bacteria	5 (17.2)	3 (33.3)	2 (10)
Gram-negative bacteria	1 (3.4)	0	1 (5)
Herpes Zoster	1 (3.4)	1 (11.1)	0
Serious adverse events			
Engraftment syndrome with GI involvement	1 (3.4)	1 (11.1)	0
Rheumatoid arthritis flare	1 (3.4)	0	1 (5)
Diarrhea	1 (3.4)	0	1 (5)
Tumor lysis syndrome	1 (3.4)	0	1 (5)

Two-year OS and PFS were 76% and 39% respectively, without treatment-emergent or increase in pre-existing peripheral neuropathy. However, a recent study by the Intergroupe Francophone Du Myeloma (IFM) 2014-02 trial randomized 300 patients receiving upfront ASCT to melphalan vs. mel/vel showing no difference in median PFS or rates of CR with a short median follow-up of 14 months [38].

Thalidomide in combination with melphalan and/or bortezomib is considered a standard regimen for induction therapy in MM [39–45]. Palumbo et al. evaluated the combination of bortezomib and thalidomide with low (50 mg/m^2) and intermediate (100 mg/m^2) dose melphalan as conditioning before salvage ASCT [46]. Response rate was 46% and was higher than that induced by the previous line of treatment in 46% of patients.

This phase I/II trial showed that high-dose melphalan with bortezomib and thalidomide is a well-tolerated ASCT conditioning regimen. High-dose thalidomide, up to 1000 mg/day, resulted in limited AEs and the MTD of thalidomide was not reached. No unexpected AEs were observed post ASCT. Response rates were encouraging with a median PFS of 9.3 months and a median OS of 65.4 months in a predominantly heavily pretreated population. Based on these findings, the combination of bortezomib and thalidomide provides a promising alternative conditioning regimen compared to single-agent melphalan for ASCT in patients with relapsed and/or refractory MM.

Nadiminti et al. performed a retrospective analysis on 100 consecutive patients receiving single or tandem ASCT in an upfront or salvage setting at a single institution using melphalan 100 mg/m^2 on days −4 and −1, borteozmib 1 mg/m^2 intravenously on days −4,−1, +2, +5, thalidomide 100 mg orally from day −4 to +5 and dexamethasone 20 mg/day orally from day −4 to day −1 and day +2 to day +5. The stringent complete remission (sCR) rate was 56%. The present trial, however, is the first to prospectively evaluate the combination of bortezomib with escalating doses of thalidomide, and dose-intense (200 mg/m^2) melphalan as ASCT conditioning. The reason for the difference in response rates between the present trial and the above trial may be related to a small proportion of salvage ASCT in the Nadiminti study, 22% compared to 58% in the present study. In addition, the patients in the present study who received upfront tandem mel/vel/thal ASCT had a suboptimal response to the first transplant, defining a functionally high-risk patient subset.

The efficacy results from the present trial are in agreement with data from earlier ASCT studies. Although the results are not substantially different from single institution and CIBMTR registry data with single-agent melphalan, the patient population of this study was intentionally selected as a cohort with primary resistance to dose-intense melphalan-based therapy. Patients who received mel/vel/thal as the second of tandem had less than a complete remission to the first ASCT, and, thus, were considered to have a suboptimal response to high-dose melphalan. The median PFS for patients who had a suboptimal response to dose-intense melphalan alone and received mel/vel/thal in the tandem setting had a median PFS and OS of 14.9 months and not reached, respectively The shorter median PFS compared to contemporary reports, and also compared to our institutional historical controls, where patients achieving less than a CR had a median PFS of 35.5 months post tandem ASCT, may be due to the smaller sample size, and also due to the higher percentage of advanced stage disease: 93% of the patients in this study were Durie Salmon Stage III differing induction, and/or maintenance regimens and our cohort's suboptimal response to high-dose melphalan. The 60-month PFS and OS rates were 15% and 51.5%, respectively. In contrast, the CIBMTR registry data for tandem ASCT showed a 60-month PFS and OS rates were 28% and 71%, respectively [24]. In the present study, the patient population is heterogeneous, the PFS post mel/vel/thal ASCT was measured without maintenance. Further, the durable OS is almost entirely accounted for by the upfront tandem population.

For the 17 patients who received a salvage mel/vel/ASCT, median PFS from their upfront ASCT was 11.9 months, compared to 9.1 months with the ⁻ salvage mel/vel/thal ASCT. Although this is a small cohort of patients, these findings appear promising considering that 60% had progression of disease just prior to the mel/vel/thal salvage ASCT, 3/17 (17.6%) had an upfront tandem ASCT, and the patients had median of three prior lines of therapy.

For all patients, the objective response rate (ORR) to their upfront melphalan ASCT was 62%, and 69% with the mel/vel/thal ASCT. Thus, for patients with a suboptimal response to high-dose melphalan alone (upfront tandem group) or as a salvage ASCT, the combination of mel/vel/thal provided a comparable depth of response. Of note, in this study, 86% were IMiD exposed and 37.9% were IMiD refractory. It is possible that the addition of bortezomib and thalidomide restored sensitivity to melphalan. The interpretation of these results may be confounded by a small cohort size and the selection of this particular cohort. In a study of salvage ASCT with melphalan 200 mg/m^2 reported by Cook et al., the ORR was 79% [30]. However, all patients received induction and/or retreatment with bortezomib, doxorubicin, and dexamethasone (PAD), and none were IMiD exposed.

This study is subject to the limitations of any prospective single-center study, which includes selection bias of patients enrolled as well as center-specific influences. The study population is heterogeneous, in regards, to disease characteristics, induction regimens and salvage regimens which may account for the significant difference between median PFS (9.3 months) and OS (65.4 months). Many of the patients did not receive their initial induction or diagnostic marrow at our center, and as such, more detailed risk stratification using cytogenetics and FISH were not available in a large subset (41%) of the patients. Although the study enrolled two different populations of patients (tandem transplant in patients with suboptimal response to the first as well as salvage transplant), this was a phase I/II study with a primary objective of evaluating safety rather than a phase 3 study where two different study populations would be of detriment to the interpretation of results.

In conclusion, our findings demonstrate that bortezomib, thalidomide, melphalan followed by ASCT is a well-tolerated conditioning regimen and a potentially valuable treatment option for MM patients who have a suboptimal response to dose-intense melphalan alone and as a salvage regimen for heavily pretreated patients, particularly in an era where most patients are exposed to upfront PI/IMiD therapy.

Compliance with ethical standards

Conflict of interest NB—Speaker's bureau for Celgene, Takeda, Amgen, and Janssen; Advisory Board for Takeda, Celgene, and Amgen; Research funding from Merck and Bristol Meyers Squibb; DHV—Speaker's bureau for Takeda, Amgen, Celgene, and Janssen; JR—Speaker's bureau for Celgene, Takeda, Janssen, Amgen, Sanofi, and BMS; DSS—Speaker's bureau for Celgene, Takeda, and Amgen; Advisory Board and Consulting for Takeda, Celgene, Amgen, and Janssen. The other authors declare that they have no conflict of interests.

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