VOLUME 28 · NUMBER 34 · DECEMBER 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bortezomib-Melphalan-Prednisone-Thalidomide Followed by Maintenance With Bortezomib-Thalidomide Compared With Bortezomib-Melphalan-Prednisone for Initial Treatment of Multiple Myeloma: A Randomized Controlled Trial

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Submitted April 9, 2010; accepted August 23, 2010; published online ahead of print at www.jco.org on October 12, 2010.

Supported by Fondazione Neoplasie Sangue Onlus.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2834-5101/$20.00

DOI: 10.1200/JCO.2010.29.8216

ABSTRACT

Purpose
The combination of bortezomib-melphalan-prednisone (VMP) is a new standard of care for newly diagnosed multiple myeloma. This phase III study examined the efficacy of the four-drug combination of bortezomib-melphalan-prednisone-thalidomide (VMPT) followed by maintenance with bortezomib-thalidomide (VMPT-VT) compared with VMP treatment alone in untreated multiple myeloma patients who are ineligible for autologous stem-cell transplantation.

Patients and Methods
A total of 511 patients were randomly assigned to receive nine cycles of VMPT followed by continuous VT as maintenance, or nine cycles of VMP at the same doses with no additional therapy. The primary end point was progression-free survival.

Results
The 3-year estimates of progression-free survival were 56% in patients receiving VMPT-VT and 41% in those receiving VMP (hazard ratio [HR], 0.67; 95% CI, 0.50 to 0.90; $P = .008$). At 3 years, the cumulative proportions of patients who did not go on to the next therapy were 72% with VMPT-VT and 60% with VMP (HR, 0.58; 95% CI, 0.50 to 0.90; $P = .007$). Complete response rates were 38% in the VMPT-VT group and 24% in the VMP group ($P < .001$). The 3-year overall survival was 89% with VMPT-VT and 87% with VMP (HR, 0.92; 95% CI, 0.53 to 1.60; $P = .77$). Grade 3 to 4 neutropenia (38% *v* 28%; $P = .02$), cardiologic events (10% *v* 5%; $P = .04$), and thromboembolic events (5% *v* 2%; $P = .08$) were more frequent among patients assigned to the VMPT-VT group than among those assigned to the VMP group; treatment-related deaths were 4% with VMPT-VT and 3% with VMP.

Conclusion
VMPT followed by VT as maintenance was superior to VMP alone in patients with multiple myeloma who are ineligible for autologous stem-cell transplantation.

J Clin Oncol 28:5101-5109. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Multiple myeloma is the second most common hematologic cancer after non-Hodgkin's lymphoma, with a higher incidence in the elderly. Patients older than age 70 years account for 66% of new cases and for 75% of all deaths from myeloma.[1] Combined melphalan-prednisone has been the reference treatment for more than 40 years and is associated with a median survival of 29 to 37 months.[2-4] Today, the availability of novel agents, such as the first in-class proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide, has significantly improved the clinical outcome of these patients.[5-12]

A meta-analysis of data for 1,682 individual patients derived from six randomized controlled trials[7-9,13,14] showed that progression-free survival (PFS) and overall survival (OS) were extended in patients who received melphalan-prednisone-thalidomide compared with those who received melphalan-prednisone alone.[15] In a large randomized

trial, bortezomib-melphalan-prednisone (VMP) was significantly superior to melphalan-prednisone for complete response (CR), time to progression, and OS at 3 years.[6] Both VMP and melphalan-prednisone-thalidomide are now regarded as the new standards of care for newly diagnosed myeloma in patients older than age 65 years.[16] In a small phase I to II study, the combination bortezomib-melphalan-prednisone-thalidomide (VMPT) was well-tolerated and effective in relapsed or refractory patients, leading to a very good partial response (VGPR) rate of 43%.[17]

Continuous therapy using an induction followed by maintenance approach has the potential to improve PFS in responding patients. Three randomized studies[18-21] explored the role of maintenance with thalidomide after autologous stem-cell transplantation, and all patients showed improvement in PFS. In a recent randomized trial,[22] maintenance with bortezomib-thalidomide significantly improved time to progression compared with that for patients who received bortezomib-prednisone. Our randomized phase III study compared a more intensive strategy based on VMPT followed by maintenance with bortezomib-thalidomide (VMPT-VT) with VMP administered for nine cycles without maintenance.

PATIENTS AND METHODS

Study Patients

Patients with newly diagnosed myeloma who were not candidates for high-dose therapy plus stem-cell transplantation because of age (≥ 65 years) or coexisting comorbidities were eligible. Inclusion criteria were measurable disease[23] and Karnofsky performance status ≥ 60%. Patients agreed to use contraception, and women of childbearing age had a pregnancy test before enrollment. Exclusion criteria included renal insufficiency (creatinine level ≥ 25 mg/L), uncontrolled or severe cardiovascular disease, psychiatric disease, any grade 2 peripheral neuropathy, and other malignancy within the past 5 years. The study was approved by the institutional review board at each of the participating centers. All patients gave written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki.

Study Design and Intervention

This randomized (1:1) phase III study was conducted at 61 centers in Italy from May 2006 to January 2009. The primary end point was PFS; secondary end points included response rate, time to the first evidence of response, OS, and incidence of any grade 3 or higher adverse events. Subgroup analyses were planned for prognostic factors.

Experimental therapy consisted of induction with nine 6-week cycles of oral melphalan 9 mg/m^2 on days 1 to 4; oral prednisone 60 mg/m^2 on days 1 to 4; intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9; and thalidomide 50 mg per day continuously. After the last VMPT course, patients received maintenance therapy with bortezomib 1.3 mg/m^2 every 14 days and thalidomide 50 mg per day for 2 years or until progression or relapse. Standard VMP therapy consisted of induction therapy with nine 6-week cycles of VMP at the same doses as previously described, without maintenance. As a consequence of the safety interim analysis, the protocol was amended to reduce the incidence of peripheral neuropathy. After the inclusion of the first 139 patients, both VMPT-VT and VMP induction schedules were changed to nine 5-week cycles and bortezomib dose was modified to 1.3 mg/m^2 on days 1, 8, 15, and 22 during cycles 1 to 9. Treatment was withheld on withdrawal of the patient's consent, disease progression, or the occurrence of any grade 4 hematologic adverse events or grade 3 to 4 nonhematologic toxic effects; less serious adverse events were managed with the use of established dose-modification guidelines.[24,25] All VMPT-VT patients received antithrombotic prophylaxis during induction at physician discretion or were allowed to participate in a randomized substudy comparing subcutaneous low-molecular-weight heparin (enoxaparin, 40 mg daily) with oral aspirin (100 mg daily) or oral warfarin (1.25 mg daily).

Assessment of End Points

PFS was calculated from the time of diagnosis until the date of progression, relapse, death for any cause, or the date the patient was last known to be in remission. Time to next therapy is part of a post hoc analysis and was calculated from the time of diagnosis until the date of subsequent myeloma

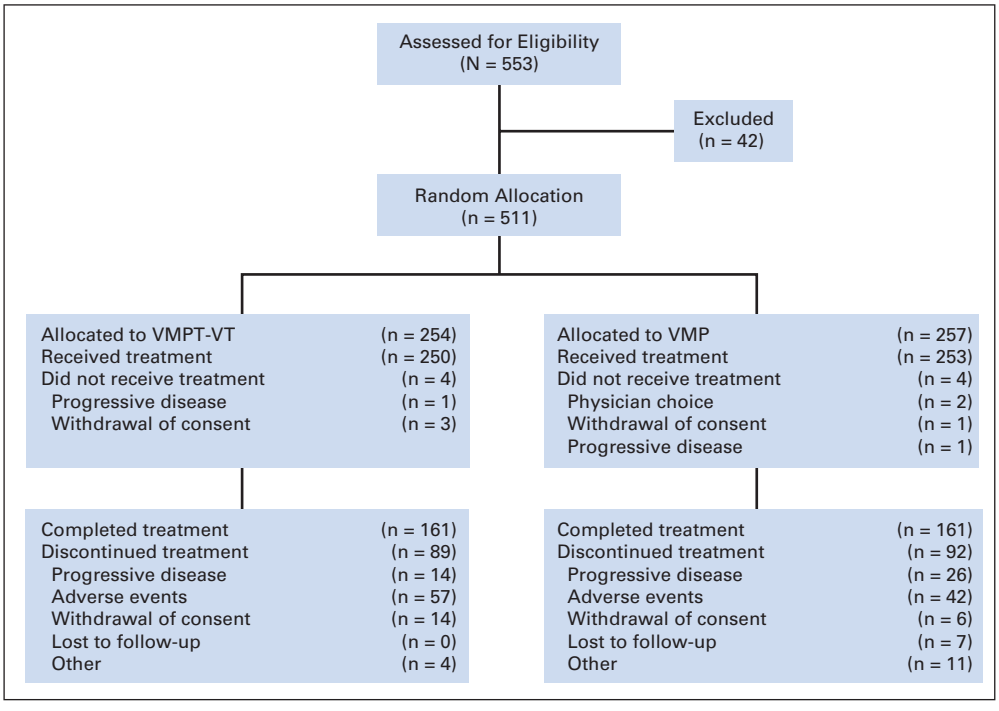

Fig 1. CONSORT diagram. VMPT-VT, bortezomib-melphalan-prednisone-thalidomide followed by maintenance therapy with bortezomib-thalidomide; VMP, bortezomib-melphalan-prednisone.

therapy administered at progression or relapse, the date of death for progressive disease, or the date the patient was last known to be in remission. OS was calculated from the time of diagnosis until the date of death for any cause or the date the patient was last known to be alive. The response to treatment was defined by using the International Uniform Response Criteria.[23] All adverse events were assessed at each visit and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0).[26]

Statistical Analysis

A sample size of 500 patients (250 per group) was determined to provide a power of 80% to detect a hazard ratio (HR) of PFS ≤ 0.75 comparing patients receiving VMPT-VT with those receiving VMP, by using a log-rank test with a two-sided alpha of .05. An interim analysis of safety was planned when approximately 80 patients had received at least one treatment. Patients were analyzed on an intention-to-treat basis for all time-to-event end points. Times of observation were censored on February 1, 2010. Response rates and safety were analyzed in patients who received at least one dose of study drugs. Response rates and the incidence of any adverse event were compared with the χ^2 test or Fisher's exact test when appropriate. Survival data were analyzed with the Kaplan-Meier method, and treatment groups were compared with the log-rank test.[27] Time to event was expressed as median with interquartile range (IQR). The Cox proportional hazard model was used to estimate the HR values and the 95% CIs for the intention-to-treat population[28] as well as within subgroups defined according to baseline characteristics to assess the consistency of treatment effects (three prespecified analyses according to albumin, β2-microglobulin, and high-risk cytogenetic profile [presence of

Table 1. Baseline Characteristics of Patients

Variable	VMPT-VT (n = 254) No.	VMPT-VT (n = 254) %	VMP (n = 257) No.	VMP (n = 257) %
Age, years				
Median	71		71	
IQR	68-75		68-75	
Subgroup				
< 65	12	5	6	2
65-74	174	68	182	71
≥ 75	68	27	69	27
Male sex	130	51	122	47
Serum β_2-microglobulin level, mg/L				
Median	3.8		4	
IQR	2.7-5.2		3.0-5.6	
Subgroup				
≤ 3.5	93	37	84	33
> 3.5	118	46	125	49
Data missing	43	17	48	18
Albumin level, g/L				
Median	37.9		37.5	
IQR	33.1-41.0		33.7-41.0	
Data missing	32	12.5	34	13
International Staging System stage				
I	59	23	56	22
II	100	39	88	34
III	47	19	57	22
Data missing	48	19	56	22
Creatinine clearance (calculated), mL/min				
< 30	21	8	24	9
30-60	147	58	160	62
> 60	86	34	73	28
LDH level, U/L				
Median	277		293	
IQR	193-355		203-368	
Data missing	51	20	36	14
Chromosome abnormalities				
Del 13	101/192*	53	86/184*	47
t(4;14)	33/192*	17	26/184*	14
t(11;14)	31/192*	16	20/184*	11
t(14;16)	9/192*	5	6/184*	3
Del17	32/192*	17	23/184*	13
Bortezomib schedule				
Twice weekly	73	29	66	26
Once weekly	181	71	191	74

Abbreviations: VMPT-VT, bortezomib-melphalan-prednisone-thalidomide followed by maintenance therapy with bortezomib-thalidomide; VMP, bortezomib-melphalan-prednisone; IQR, interquartile range; LDH, lactate dehydrogenase.
*Number of patients presenting the abnormality out of the total number of patients analysed per group.

a t(4;14), t(14,16), or a 17p deletion] and five post hoc analyses according to sex, age, creatinine clearance, lactate dehydrogenase, and bortezomib schedule). Subgroup analyses were performed by introducing an interaction term between the treatment group variable and the subgroup variables.

RESULTS

Two hundred fifty-four patients were randomly assigned to receive VMPT-VT and 257 to receive VMP. About two thirds of patients completed the assigned induction treatment schedule (Fig 1). Baseline demographic and disease characteristics were balanced between the two groups (Table 1), the median age was 71 years, and 27% of patients were older than age 75 years in both groups.

Efficacy

After a median follow-up from diagnosis of 23.2 months (IQR, 17.1 to 32.1 months), median PFS was not reached in the VMPT-VT group and was 27.3 months (IQR, 17.5 to not reached) in the VMP group. The 3-year PFS rate was 56% in patients receiving VMPT-VT and 41% in patients receiving VMP, corresponding to a 33% relative reduction of risk of progression in the VMPT-VT group (HR, 0.67; 95% CI, 0.50 to 0.90; $P = .008$; Fig 2A). The PFS benefit of the VMPT-VT group was quite similar among subgroups defined by creatinine clearance, baseline β2-microglobulin level, albumin level, and bortezomib schedule; small and not significant differences were detected among subgroups defined by age, clinical stage, and cytogenetic risk, although a more pronounced difference was observed by sex ($P = .02$), with the advantage for VMPT-VT limited to female patients (Fig 3). We analyzed the main prognostic factors (age, International Staging System [ISS],[29] chromosomal abnormalities, bortezomib schedule, and creatinine clearance) between VMPT-VT and VMP among male and female patients, and no differences were detected.

CR, VGPR, and partial response rates were higher with VMPT-VT (Table 2). During induction therapy, CR rate was 38% with VMPT-VT and 24% with VMP ($P < .001$), VGPR rate or better was 59% with VMPT-VT and 50% with VMP ($P = .03$). An exploratory analysis was performed on the 82 patients treated with VMPT-VT who received at least 6 months of maintenance with VT: the nine cycles of induction with VMPT resulted in 62 patients (76%) with at least VGPR, including 48 patients (58%) with CR; VMPT followed by at least 6 months of VT treatment resulted in 63 patients (77%) with at least VGPR, including 51 patients (62%) with CR.

At 3 years, the cumulative proportions of patients who did not proceed to the next therapy were 72% with VMPT-VT and 60% with VMP (HR, 0.58; 95% CI, 0.39 to 0.87; $P = .007$; Fig 2B). Fifty-one patients had died: 24 (9%) in the VMPT-VT and 27 (11%) in the VMP group. The 3-year OS rate was 89% in the VMPT-VT group and 87% in the VMP group (HR, 0.92; 95% CI, 0.53 to 1.60; $P = .77$; Fig 2C).

Adverse Events

The two study groups did not differ significantly in the rates of treatment-related deaths: nine patients (4%) died in the VMPT-VT group and seven (3%) in the VMP group ($P = .59$), mainly due to cardiac, pulmonary, and infective complications. Table 3 lists the grade 3 to 4 adverse events during induction. The incidence of any grade 3 to 4 hematologic adverse events was similar in the two groups, but severe neutropenia was more frequent with treatment by

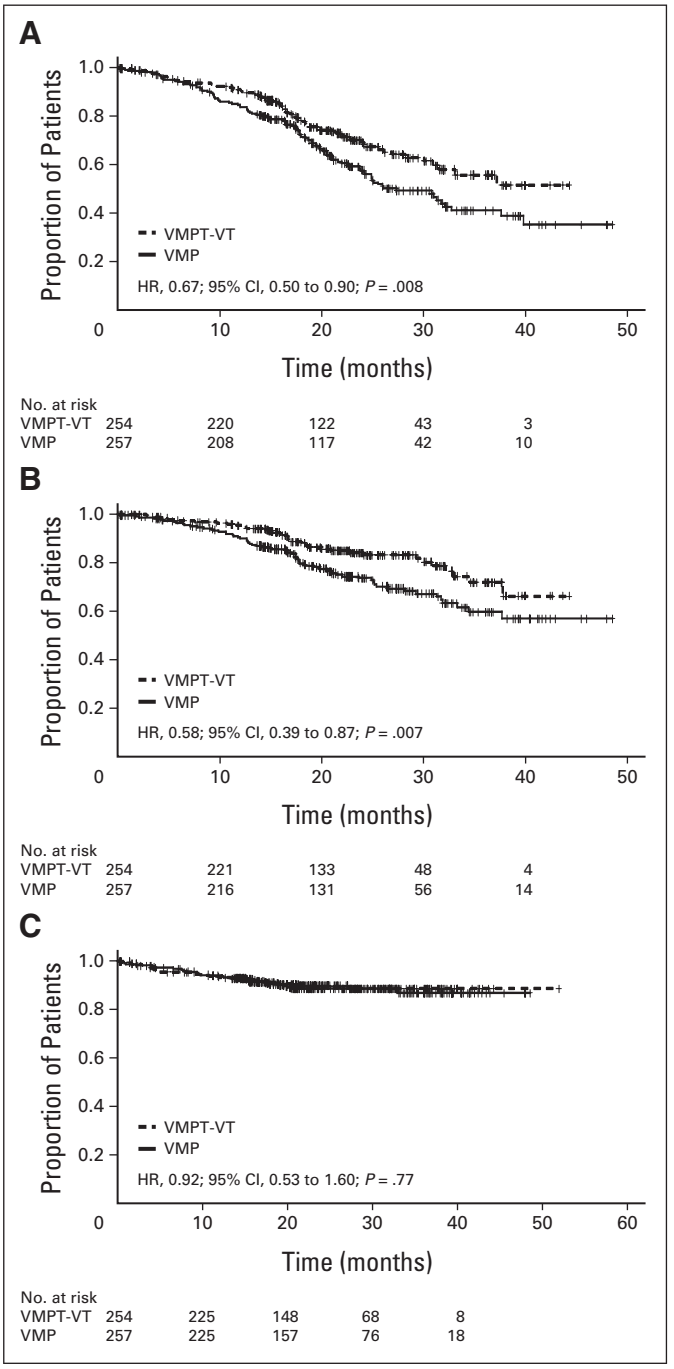

Fig 2. Kaplan-Meier curves for the progression-free survival, time to next therapy, and overall survival in the intention-to-treat population. (A) Progression-free survival. The median progression-free survival was not yet reached in the bortezomib-melphalan-prednisone-thalidomide followed by maintenance therapy with bortezomib-thalidomide (VMPT-VT) group and was 27.3 months (interquartile range [IQR] 17.5 months to not reached) in the bortezomib-melphalan-prednisone (VMP) group. (B) Time to next therapy. The median time to next therapy was not reached in either group: 3-year rate was 72% in the VMPT-VT group and 60% in the VMP group. (C) Overall survival after a median follow-up of 23.2 months (IQR, 17.1 to 32.1 months). Median survival was not reached in either group. During that time, 24 patients (9%) in the VMPT-VT group and 27 patients (11%) in the VMP group died. HR, hazard ratio.

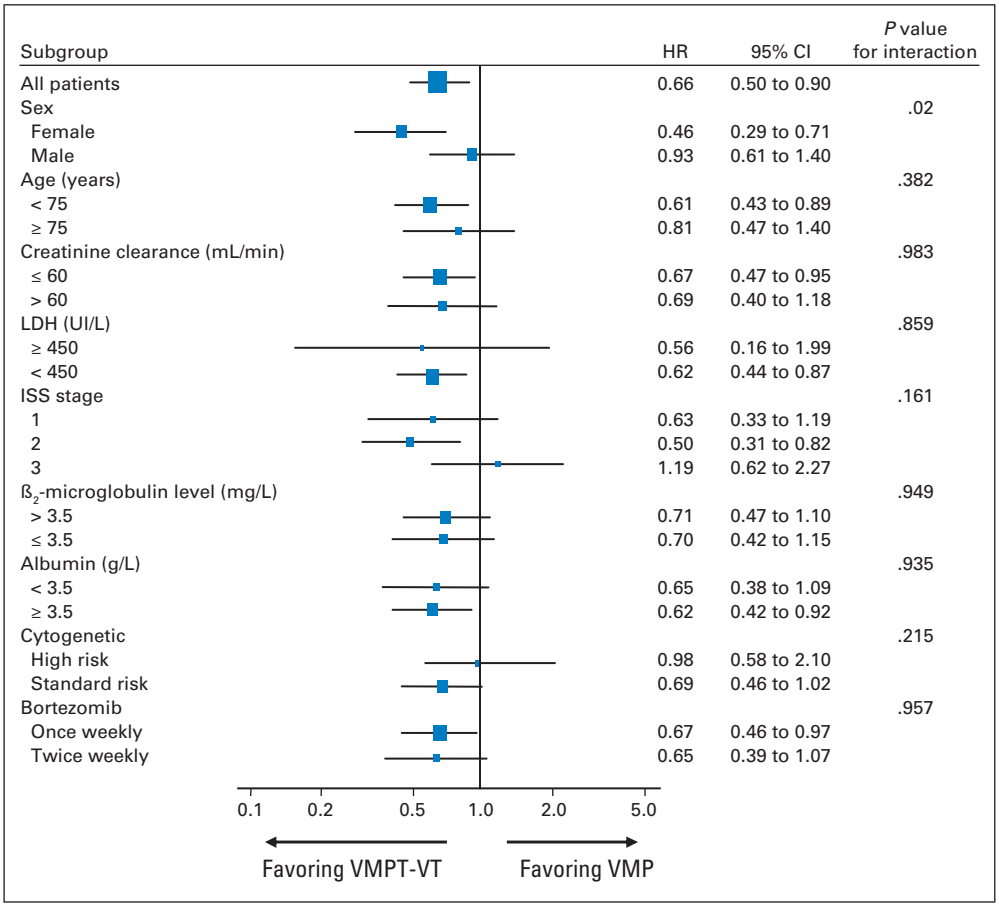

Fig 3. Subgroup analysis of progression-free survival. Analyses of the progression-free survival among subgroups of patients, as defined according to baseline demographic and disease characteristics. Hazard ratios (HRs) lower than 1 indicate a lower risk of progression. High cytogenetic risk was defined as t(4;14) or t(14;16) or del17. The horizontal bars represent 95% CIs. LDH, lactate dehydrogenase; ISS, International Staging System; VMPT-VT, bortezomib-melphalan-prednisone-thalidomide followed by maintenance therapy with bortezomib-thalidomide; VMP, bortezomib-melphalan-prednisone.

VMPT-VT (38% *v* 28%; $P = .02$). Grade 3 to 4 cardiac complications were more frequent in patients receiving VMPT-VT (10% *v* 5%; $P = .04$) and were mainly due to arrhythmia, cardiac failure, and myocardial infarction or angina. Grade 3 to 4 thromboembolic events were slightly more frequent in patients receiving VMPT-VT (5% *v* 2%; $P = .08$) and consisted of deep vein thrombosis and pulmonary embolism. The incidence of severe infections was similar in both groups (13% *v* 9%; $P = .18$) and mainly due to pneumonia and neutropenic fever; grade 3 to 4 herpes zoster was < 1% in both groups. Grade 3 to 4 sensory neuropathy was reported in 8% of patients receiving VMPT-VT and in 5% of patients receiving VMP ($P = .19$); neuralgia was reported in 4% of patients receiving VMPT-VT and 3% of patients receiving VMP ($P = .59$). During maintenance with VT, seven patients (8%) experienced at least one grade 3 to 4 adverse event. The incidence of neuropathy did not increase: only three patients (4%) developed grade 3 peripheral neuropathy, and no grade 4 neuropathies were reported. One patient (1%) experienced a grade 4 cardiac complication (pericardial effusion).

The proportion of patients requiring treatment interruption for adverse events was similar in the two groups ($P = .10$). In the VMPT-VT group, 57 patients (23%) discontinued treatment for adverse events; the major causes of discontinuation were peripheral neuropathy (21 patients), hematologic toxicity (nine patients), cardiac or pulmonary complication (nine patients), infection (six patients), and thrombosis (three patients). In the VMP group, 42 patients (17%) discontinued treatment for adverse events mainly for peripheral neuropathy (19 patients), hematologic toxicity (10 patients), infection (five patients), cardiac or pulmonary complication (four patients), and thrombosis (one patient).

Bortezomib Schedule

In the exploratory analysis of 134 patients receiving twice-weekly bortezomib compared with 369 patients on the once-weekly schedule, the 3-year PFS rate was 47% versus 50%, respectively (HR, 1; 95% CI, 0.73 to 1.37; $P = 1.00$); the CR rate was 35% versus 30%, respectively ($P = .27$); and the 3-year OS rate was 89% versus 88%, respectively (HR, 1.22; 95% CI, 0.64 to 2.31; $P = .54$).

In patients receiving twice-weekly bortezomib, nonhematologic grade 3 to 4 adverse events were reported in 68 (51%). In those receiving once-weekly bortezomib, grade 3 to 4 nonhematologic adverse events were observed in 131 patients (36%); the reduction was significant ($P = .003$) and was mainly related to severe sensory peripheral neuropathy that was reduced from 16% to 3% ($P < .001$), without any significant difference in the VMPT-VT and VMP groups. No other significant differences were observed.

The once-weekly schedule of bortezomib reduced the discontinuation rate and prolonged the time on therapy: in both groups, patients received a median of nine cycles but the median cumulative delivered dose of bortezomib was similar—40.1 mg/m^2 for twice-weekly and 39.4 mg/m^2 for once-weekly regimens—corresponding to a dose intensity of 59% for twice-weekly and 84% for once-weekly regimens.

Table 2. Best Response to Induction Treatment and Time-to-Event Data

Response and Time-to-Event	VMPT-VT Group (n = 250) No.	VMPT-VT Group (n = 250) %	VMP Group (n = 253) No.	VMP Group (n = 253) %	*P*
Best response according to International Uniform Response Criteria					
Complete, very good partial, or partial response	222	89	205	81	.01
Complete response	95	38	61	24	< .001
Very good partial response	53	21	65	26	
Partial response	74	30	79	31	
Stable disease	16	6	43	17	
Progressive disease	3	1	2	1	
Time-to-event					
Time to response, months					
Partial response					.21
Median	1.4		1.4		
Range	1.1-2.3		1.1-2.3		
Complete response					.12
Median	5.5		4.6		
Range	3.4-8.0		2.8-6.9		
Duration of response					
Complete or partial response					
Median, months	N/R		28.4		.02
Range, months			16.4-N/R		
Patients in remission at 2 years	54	69	40	53	.02
Complete response					
Median, months	N/R		N/R		.83
Range, months	24.3-N/R		27.0-N/R		
Patients in remission at 2 years	29	76	16	79	.83

NOTE. A total of eight patients (four in each study group) could not be evaluated for a response because they did not receive a study drug because of withdrawal of consent (three patients in the VMPT-VT group [bortezomib-melphalan-prednisone-thalidomide followed by maintenance therapy with bortezomib-thalidomide] and one in the VMP group [bortezomib-melphalan-prednisone]), progressive disease (one patient in each group), or physician choice (two patients in the VMP group). Among the patients who could be evaluated, responses were not determined for nine patients in the VMPT-VT group and three in the VMP group. Percentages may not total 100 because of rounding.
Abbreviation: N/R, not reached.

DISCUSSION

In newly diagnosed myeloma patients ineligible for autologous stem-cell transplantation, we compared VMPT-VT, a rational combination of four drugs exploiting potential synergies and minimizing overlapping toxicities followed by maintenance, with the standard VMP without maintenance. VMPT-VT was superior to VMP in terms of CR and PFS, but an OS benefit was not apparent. In the VMPT-VT group, the reduced risk of progression was 33% compared with that for the VMP group (HR, 0.67; $P = .008$) while the reduced risk of time to next therapy was 42% (HR, 0.58; $P = .007$). The introduction of the once-weekly infusion of bortezomib significantly reduced the risk of peripheral neuropathy. The VMPT-VT regimen increased thromboembolism and cardiologic toxicity, particularly in patients age $\geq$ 75 years.

In the Velcade as Initial Standard Therapy in Multiple Myeloma (VISTA) study, the addition of bortezomib to melphalan-prednisone reduced the risk of progression by 54% compared with melphalan-prednisone alone.[6] In this trial, the addition of thalidomide to VMP reduced the risk of progression by 33% compared with VMP alone. Although it is difficult to make cross comparisons between different trials because of differences in the study populations, the dose intensity, or use of maintenance, the median PFS with VMP was 21.7 months in the VISTA study and 27.3 months in our study. The additional advantage in our study may be attributed to the adoption of a weekly infusion of bortezomib that significantly reduced the rate of discontinuation due to adverse events.

For male patients, and to a lesser degree, for those older than age 75 years, VMPT-VT seemed not to add any significant advantage to VMP. The small number of patients precluded a meaningful analysis of the relation between baseline prognostic factors and outcome related to sex. Recent larger population-based studies[30,31] on patients with cancer showed a higher survival among women for all tumor types and especially for melanoma and lung cancer. Sex-related differences in myeloma patients should be analyzed in future and broader studies. In elderly patients, higher dose intensity enhanced efficacy but may considerably increase toxicity and discontinuation rate, limiting the net benefit of therapy in frail patients. Since biologic and chronologic age do not always correspond, a careful geriatric assessment should be adopted to tailor treatment in frail patients who could benefit from a gentler approach. The outcome of high-risk patients, such as those with ISS 3 or with chromosomal abnormalities, was similar in patients receiving VMPT-VT or VMP. By contrast, the outcome of standard-risk patients was superior with VMPT-VT. Additional studies are needed to assess whether more is better in standard-risk than in high-risk patients. Several studies[32-34] showed that CR is an important surrogate of outcome and considerably increases remission duration. In the VMPT-VT group, the rate of CR

Table 3. Grade 3 to 4 Adverse Events During Induction Treatment

Event	VMPT-VT Group (N = 250) No.	%	VMP Group (N = 253) No.	%	P
Hematologic events	117	47	104	41	.20
Neutropenia	95	38	71	28	.02
Thrombocytopenia	54	22	50	20	.61
Anemia	25	10	25	10	.96
Nonhematologic events	115	46	84	33	.003
Cardiologic events	26	10	14	5	.04
Myocardial infarction/angina	4		5		
Arrhythmia	10		2		
Cardiac failure	7		4		
Other	5		3		
Nervous system disorder	41	16	39	15	.76
Sensory neuropathy	20	8	13	5	.19
Neuralgia	9	4	7	3	.59
Sensory neuropathy and neuralgia	8		11		
Ictus/syncope	0		4		
Confusion	2		0		
Mood depression	0		2		
Other	2		2		
Infections	32	13	23	9	.18
Pneumonia	14		6		
Neutropenic fever	6		5		
Viral infection	3		1		
Sepsis	4		5		
Other	5		6		
GI events	16	6	21	8	.41
Diarrhea	4		7		
Constipation	6		5		
Nausea/vomiting	2		3		
Other	4		6		
Vascular events	13	5	5	2	.05
Deep vein thrombosis	8		5		
Pulmonary embolism	4		0		
Peripheral edema	1		0		
Systemic events	16	6	8	3	.09
Fatigue	15		5		
Fever	1		3		
Dermatologic events	9	4	6	2	.42
Rash	9		5		
Sweet syndrome	0		1		
Bleeding	1	<1	1	<1	.99
Other conditions	14	6	13	5	.87

NOTE. A total of eight patients, four in each study group, could not be evaluated for adverse events because they did not receive a study drug because of withdrawal of consent (three patients in the VMPT-VT group [bortezomib-melphalan-prednisone-thalidomide followed by maintenance therapy with bortezomib-thalidomide] and one in the VMP group [bortezomib-melphalan-prednisone]), progressive disease (one patient in each group), or physician choice (two patients in the VMP group).

was 38%, significantly higher than 24% in the VMP group. Few patients had a further improvement in response rate during the first 6 months of maintenance with VT, suggesting that the major influence on response rate was determined by the nine cycles of induction therapy.

We have demonstrated that a more intense approach, including the four-drug combination followed by maintenance, VMPT-VT, is superior to the VMP schema. The benefit of maintenance after VMPT could not be assessed by our study because of the absence of a second random assignment after induction and the relatively short follow-up. Evidence of the efficacy of thalidomide as maintenance has been provided by other phase III trials.[18-21] In a Spanish randomized study, maintenance with VT prolonged remission duration in comparison with bortezomib-prednisone.[22] Other studies[35-37] on bortezomib as maintenance or consolidation therapy supported the feasibility and the efficacy of this approach.

Lenalidomide as maintenance therapy showed encouraging results in both young and elderly patients.[38-41] The combination lenalidomide-bortezomib-dexamethasone showed promising results, with an overall response rate of 100%.[42] Maintenance with lenalidomide as well as consolidation with bortezomib plus lenalidomide may be considered other options for future treatment.

Both VMPT-VT and VMP regimens were well tolerated. Hematologic toxicities were similar in both groups with the exception of neutropenia that was increased by the addition of thalidomide. The incidence of grade 3 to 4 cardiac adverse events was significantly higher in patients receiving VMPT-VT, especially in those older than age 75 years. A full cardiologic work-up before starting thalidomide treatment seems appropriate to detect asymptomatic cardiologic abnormalities or increased risk of thromboembolic events. The incidence of infections was slightly increased in patients receiving thalidomide. A more careful assessment of fevers of unknown origin and prompt administration of antibiotic prophylaxis might reduce the risk of infection. The incidence of thromboembolism was 5% in patients receiving VMPT-VT with antithrombotic prophylaxis and 2% in those receiving VMP without any prophylaxis. These data provide further support to the protective role of bortezomib against thrombosis and confirm the efficacy of current standard antithrombotic prophylaxes for thalidomide.[43,44]

In conclusion, this study showed that VMPT-VT was superior to VMP, one of the latest and more effective standards of care for elderly patients in terms of response rate and PFS. Moreover, our findings suggest that weekly infusion of bortezomib is a valuable treatment.

In both groups, the once-weekly infusion of bortezomib significantly reduced the incidence of severe sensory peripheral neuropathy from 16% to 3%. This unprecedented improvement in safety came with no reduction in efficacy, probably because of a similar delivered dose of bortezomib in both groups. The weekly schedule of bortezomib reduced the rate of discontinuation and prolonged the time on therapy with positive effects on the length of remission.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Antonio Palumbo, Celgene (C), Janssen-Cilag (C); Sara Bringhen, Merck Sharp & Dohme (C); Mario Boccadoro, Celgene (C), Janssen-Cilag (C) **Stock Ownership:** None **Honoraria:** Antonio

Palumbo, Celgene, Janssen-Cilag; Sara Bringhen, Celgene, Janssen-Cilag, Novartis; Massimo Offidani, Celgene, Janssen-Cilag; Francesca Patriarca, Celgene, Janssen-Cilag, Shering-Plough, Roche; Daniela Gottardi, Janssen-Cilag; Pellegrino Musto, Celgene, Janssen-Cilag; Maria Teresa Petrucci, Celgene, Janssen-Cilag **Research Funding:** Luca Baldini, Celgene, Janssen-Cilag; Pellegrino Musto, Celgene; Mario Boccadoro, Celgene, Janssen-Cilag **Expert Testimony:** None **Other Remuneration:** None

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