CME article

Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma

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The Intergroupe Francophone du Myelome conducted a randomized trial to compare bortezomib-dexamethasone (VD) as induction before high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) to a combination consisting of reduced doses of bortezomib and thalidomide plus dexamethasone (vtD) in patients with multiple myeloma. Overall, a total of 199 patients were centrally randomly assigned to receive VD or vtD. After 4 cycles, the complete response (CR) rate was the same in both groups (13% in the vtD arm, 12% in the VD arm, $P = .74$). However, the CR plus very good partial response (VGPR) rate was significantly higher in the vtD arm (49% vs 36%, $P = .05$). After ASCT, the CR plus VGPR rate was significantly higher in the vtD arm (74% vs 58%, $P = .02$). The reduced doses of bortezomib and thalidomide translated into a reduced incidence of peripheral neuropathy (PN): grade ≥ 2 PN were reported in 34% in the VD arm versus 14% in the vtD arm ($P = .001$). vtD, including reduced doses of bortezomib and thalidomide, yields higher VGPR rates compared with VD and can be considered a new effective triplet combination before HDT/ASCT. This study was registered with www.clinicaltrials.gov as #NCT00910897 and EudraCT as #2007-005204-40. (*Blood*. 2011;118(22):5752-5758)

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Disclosures

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Learning objectives

Upon completion of this activity, participants will be able to:

1. Compare complete response (CR) rate with VD versus vtD as induction prior to HDT and ASCT in patients with multiple myeloma.
2. Compare the CR plus very good partial responses (VGPR) rate with VD versus vtD as induction prior to HDT and ASCT in patients with multiple myeloma.
3. Compare the safety with VD versus vtD as induction prior to HDT and ASCT in patients with multiple myeloma.

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Introduction

Until now, high-dose therapy plus autologous stem cell transplantation (HDT/ASCT) is considered the standard of care for the frontline treatment in younger patients with multiple myeloma (MM).[1] In the context of HDT/ASCT, achievement of complete response (CR) or at least very good partial response (VGPR) is associated with an improved outcome.[2-5] One strategy to increase the CR plus VGPR rate in the HDT/ASCT paradigm is to improve the induction treatment. Before the era of novel therapies, induction treatment typically consisted of high-dose dexamethasone alone or combined with vincristine and adriamycin (VAD). Compared with dexamethasone or VAD, the combination of thalidomide and dexamethasone as induction treatment increased the overall response rate but failed to increase the CR rate before HDT/ASCT or the CR plus VGPR rate after ASCT.[6,7] A randomized trial conducted by the Intergroupe Francophone du Myelome (IFM) showed that, compared with VAD, bortezomib plus dexamethasone (VD) significantly increased the CR plus VGPR rate both before and after HDT/ASCT across all prognostic subgroups[8] and may therefore be considered a new standard induction treatment. Three-drug combinations, including one novel agent, have also been found to be superior to VAD or VAD-like regimens,[9-11] but the most promising results have been obtained with a 3-drug regimen consisting of thalidomide, bortezomib, and dexamethasone.[12,13] However, the use of bortezomib and thalidomide as part of induction regimens is associated with a risk of developing peripheral neuropathy (PN), which may be disabling and may hamper further treatment with these agents. Therefore, the objective of any new induction regimen should be to provide the best efficacy/toxicity ratio. The IFM conducted a phase 3 randomized trial to compare VD with a combination consisting of reduced doses of bortezomib and thalidomide plus dexamethasone (vtD). The objectives of the study were to determine whether the addition of thalidomide to bortezomib and dexamethasone would improve the CR and CR plus VGPR rates compared with VD and whether the reduced doses of bortezomib and thalidomide would reduce the incidence of PN.

Methods

Patients

Eligible patients were 65 years of age or younger and had untreated symptomatic MM with measurable paraprotein in serum (> 1 g/dL) or urine (> 0.2 g/24 hours). Key inclusion criteria were Eastern Cooperative Oncology Group performance status ≤ 2, and adequate renal function.

Key exclusion criteria included confirmed amyloidosis, HIV positivity, history of other malignancy (other than basal cell carcinoma and carcinoma of the cervix in situ), uncontrolled diabetes, and grade ≥ 2 peripheral neuropathy (National Cancer Institute Common Toxicity Criteria Version 2.0).

All patients provided written informed consent. The study was approved by the relevant national health authority agency and the French national ethics committee and was conducted in accordance with the International Conference on Harmonization of Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki.

Study design

This open-label phase 3 randomized trial was conducted at 50 IFM centers from March 2008 to January 2009. The data cut-off date for this report was December 31, 2010. Patients were centrally randomized to receive 4 cycles of VD or vtD, followed by 1 cycle of high-dose melphalan plus ASCT. Patients were stratified by baseline β_2-microglobulin (> 3 vs ≤ 3 mg/L) and chromosome 13 abnormalities (presence vs absence) by FISH analysis.

VD consisted of four 3-week cycles of bortezomib 1.3 mg/m^2 administered intravenously on days 1, 4, 8, and 11 plus dexamethasone 40 mg days 1-4 (all cycles) and days 9-12 (cycles 1 and 2). vtD was composed of four 3-week cycles of bortezomib 1 mg/m^2 on days 1, 4, 8, and 11, thalidomide 100 mg/day administered orally, and dexamethasone at the same dose and schedule as for the VD regimen. In case of less than partial response (PR) after cycle 2, the dose of bortezomib was increased to 1.3 mg/m^2 and the dose of thalidomide to 200 mg/day in the vtD arm. Recommended concomitant medications included bisphosphonates, antibiotics, and antiviral prophylaxis in accordance with local practice.

Stem cells were mobilized with G-CSF 10 μg/kg from day 15, cycle 3. If collection was inadequate, a second mobilization was undertaken with cyclophosphamide 3 g/m^2 plus G-CSF 5 μg/kg. Target yield was 2×10^6 CD34$^+$ cells/kg. Conditioning for ASCT consisted of melphalan 200 mg/m^2. Peripheral neuropathy signs or symptoms were managed according to established guidelines.[8]

Assessment

The primary endpoint was postinduction CR rate. Secondary end points were CR plus VGPR rates after cycle 2, after induction, and after ASCT; overall response rates ($\geq$ PR) after cycle 2, after induction, and after ASCT; and safety and toxicity of induction, including incidence of PN. Patients withdrawn before response evaluation for progression, toxicity requiring treatment cessation, and consent withdrawal were considered as nonresponders. In addition, patients who could not receive ASCT and those who received salvage treatment or additional therapies before ASCT were also considered as nonresponders. Blood and 24-hour urine samples were taken at baseline, before each induction cycle, at ASCT and 1 to 3 months after ASCT. Blood and 24-hour urine electrophoresis samples were analyzed centrally (HAL) at baseline, after cycle 2, after cycle 4, and after ASCT. Response was evaluated centrally according to International Myeloma Working Group Uniform Criteria.[14] Adverse events were graded by National Cancer Institute Common Toxicity Criteria Version 2.0. Data were monitored by an external CRO.

Statistical analysis

Considering the CR rate obtained with VD in the IFM 2005-01 trial[8] and the CR rate obtained in the first experience with VTD in newly diagnosed patients,[15] 200 patients were to be enrolled. This provided 80% power

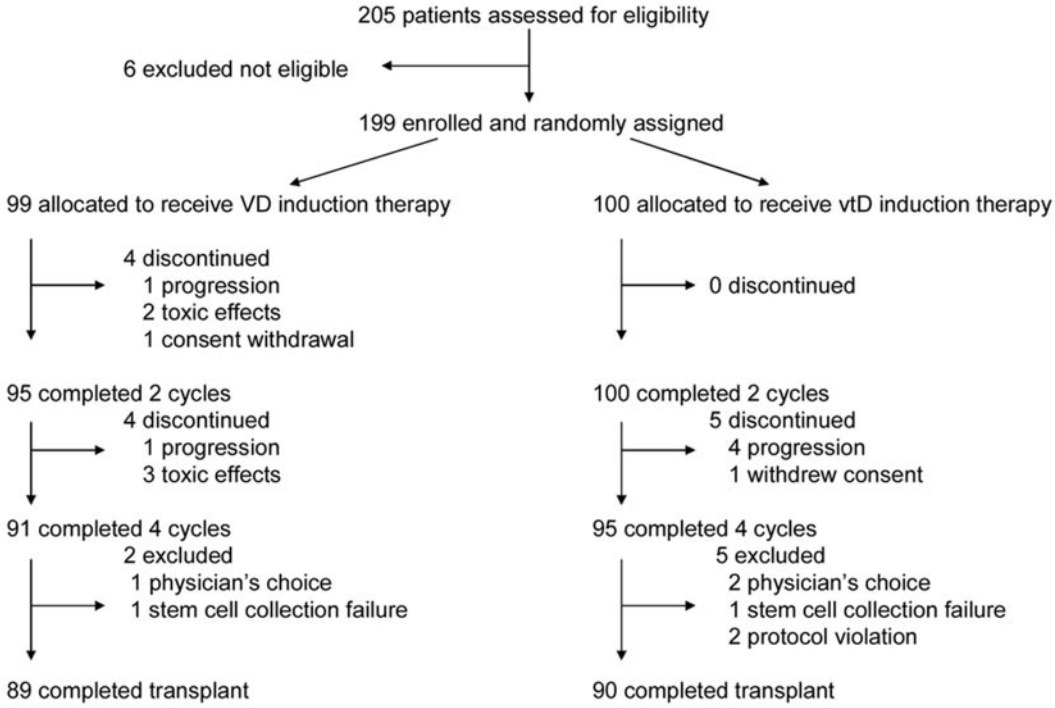

Figure 1. Trial profile.

(2-sided test with type I error of .05) to detect an 18% difference in postinduction CR rate, assuming a CR rate of 7% with VD. Comparisons of the CR rates, including the primary endpoint (postinduction CR rate) were performed using a χ^2 test, and differences in CR rates were expressed as proportions with corresponding 95% confidence intervals (CIs).

For the postinduction CR and CR plus VGPR rates, prognostic factors for response were looked for using logistic regression analysis, adjusted for treatment to check whether the absence or the presence of a difference between the response rates for vtD and VD was confirmed when taking into account factors significantly related to response. The following factors were tested: stratification criteria used in the initial randomization process, β_2-microglobulin level, chromosome 13 deletion, translocation t(4;14), 17p deletion, International Staging System, performance status, and second mobilization with cyclophosphamide. First, each factor was studied using univariable logistic regression analysis. Second, all factors with a P value $< .20$ were examined in a multivariable logistic model, using the likelihood ratio test for factor selection in a backward selection procedure. Factors with a P value $< .05$ were kept in the final model.

Descriptive data on the use of consolidation and maintenance treatment, which was administered at the physician's discretion, were collected. Progression-free survival curves from the date of randomization were estimated using the Kaplan-Meier method and compared between vtD and VD using a log-rank test.

Results

Patient characteristics and disposition

A total of 205 patients provided written informed consent, and 6 of these were withdrawn from the analysis because of violation of inclusion criteria. Overall, a total of 199 patients were randomly assigned to receive VD (99 patients) or vtD (100 patients; Figure 1). Baseline characteristics are summarized in Table 1. No significant difference was observed between the 2 groups, although the proportion of patients with t(4;14) and/or del (17p) was higher in the vtD arm (26%) than in the VD arm (15%; $P = .08$).

Response to induction and HDT

After the first 2 cycles, 90% of patients in the vtD arm had achieved at least a PR versus 77% in the VD arm ($P = .01$; Table 2). The difference in overall response rate between the vtD and VD arms was 13% (95% CI, 3%-24%). As a consequence, the doses of bortezomib and thalidomide had to be increased for the last 2 cycles in only 7 patients in the vtD arm. In 1 case, response was downgraded despite increased doses of thalidomide and bortezomib (from stable disease [SD] to progression), in 1 case response remained stable, whereas in 5 cases responses were upgraded (from SD to PR in 3, and from SD to CR in 2 patients).

After 4 cycles, the CR rate was the same in both groups (13% in the vtD arm, 12% in the VD arm, $P = .74$; Table 2). However, the CR plus VGPR rate was significantly higher in the vtD arm (49% vs 36%, $P = .05$). The difference in CR plus VGPR rates between the vtD and VD arms was 13% (95% CI, 0%-27%). The overall response rate was 88% in the vtD arm versus 81% in the VD arm ($P = .19$). The use of cyclophosphamide to mobilize stem cells did not upgrade the response to induction therapy in either arm of the study.

After one course of high-dose melphalan 200 mg/m^2 and ASCT, there was no difference in the CR rate between the vtD arm (29%) and the VD arm (31%; $P = .77$), whereas the CR plus VGPR rate was significantly higher in the vtD arm (74% vs 58%, $P = .02$). The difference in CR plus VGPR rates between the vtD and VD arms was 16% (95% CI, 3%-30%). The overall response rate was 89% in the vtD arm versus 86% in the VD arm ($P = .54$).

Prognostic factors for response

As shown in Table 3, none of the analyzed factors was predictive for CR plus VGPR.

Stem cell mobilization and transplantation

A total of 181 patients (90 in the VD arm, 91 in the vtD arm) underwent stem cell mobilization as stated in the protocol. After

Table 1. Patient characteristics

	VD (n = 99)	VTD (n = 100)	P*
Median age, y (IQR)	57 (52-61)	58 (54-62)	.28
Male/female	60/39	55/45	.42
Albumin, g/L, median (IQR)	36.9 (30.3-41.5)	35.7 (31.5-41.5)	.77
Missing	3	2	
β_2-microglobulin, mg/L, median (IQR)	3.6 (2.7-5.3)	3.8 (2.6-5.1)	.99
International Staging System, no. %			
1	33 (34)	31 (31)	.9
2	43 (44)	46 (46)	
3	21 (22)	23 (23)	
Missing	2	0	
Calcium level, mg/L, median (IQR)	93 (89-99)	97 (90-101)	.16
Creatinine level, mM/L, median (IQR)	88 (71-103)	88 (71-101)	.68
t(4,14) or del17p, no. %	12 (15)	21 (26)	.08
Missing	18	19	
Performance status, %			
0	49	48	.2
1	44	44	
2	3	7	
3 or 4	3	0	
Missing	0	1	
Hemoglobin level, g/dL, median (IQR)	11.3 (9.4-12.7)	11.3 (9.9-12.8)	.47
White blood cell count, 10^9/L, median (IQR)	5.8 (4.4-7.5)	6.0 (5.0-8.1)	.32
Platelet count, 10^9/L, median (IQR)	253 (192-297)	229 (177-289)	.20

IQR indicates interquartile range.
*χ^2 or Wilcoxon test.

priming with G-CSF alone, the median number of $CD34^+$ cells/kg was 7.4×10^6 in the VD arm versus 6.4×10^6 in the vtD arm ($P = .002$). The number of aphereses (mean ± SD) was 2.0 ± 1.1 in the VD arm versus 2.6 ± 1.2 in the vtD arm ($P < .001$). The target yield of 2×10^6 $CD34^+$ cells/kg was achieved in 93% and 80% of VD and vtD patients, respectively ($P = .01$). The final failure rate after second mobilization with cyclophosphamide plus G-CSF or plerixafor was 1% in both arms of the study.

A total of 179 patients (89 in the VD arm, 91 in the vtD arm) underwent HDT/ASCT as stated in the protocol. The duration of hospitalization (mean ± SD) was 19.8 ± 4.5 days in the VD arm and 18.7 ± 3.4 days in the vtD arm ($P = .04$). The duration (mean ± SD) of neutropenia ($< 0.5 \times 10^9$/L) and of thrombocytopenia ($< 50 \times 10^9$/L) was 5.9 ± 2.2 days versus 6.5 ± 3.9 days ($P = .32$), and 7.1 ± 3.9 days versus 8.0 ± 6.6 days ($P = .97$) in the VD and vTD arms, respectively. There was no toxic death during the HDT/ASCT procedure.

Safety

The safety population included all 199 patients (99 in the VD arm, 100 in the vtD arm) who had received at least 1 dose of bortezomib and/or thalidomide.

As shown in Table 4, the proportion of patients with at least 1 adverse event or adverse events ≥ grade 3 was not different between the 2 groups. Grade 3 or 4 hematologic or nonhematologic (with the exception of PN) toxicities were rare, with no significant differences between VD and vtD. The overall proportion of patients demonstrating signs or symptoms that were compatible with the diagnosis of PN was 70% in the VD arm versus 53% in the vtD arm ($P = .01$). Moreover, with a rate of 34% ≥ grade 2, the severity of PN was much higher in the VD arm than in the vtD arm in which the rate of ≥ grade 2 was only 14% ($P = .001$). Grade 3 PN was seen in 11% of cases with VD and in only 3% with vtD ($P = .03$), and 4 patients had to discontinue induction treatment because of PN in the VD arm versus none in the vtD arm.

Outcome: progression-free and overall survival

The aim of the study was to compare induction therapy; therefore, per protocol, no recommendation was provided regarding post-ASCT therapy. Subsequent consolidation and maintenance treatment was at the physician's discretion and varied widely in the 2 arms of the study. A higher number of consolidation treatments were applied in the VD arm overall (n = 24 vs n = 16 in the vtD arm). These consisted of a second ASCT in 7 cases (vs 4), 2 cycles of lenalidomide (25 mg/day, 21 and 28 days) in 10 cases (vs 7), and 2 cycles of vtD in 7 cases (vs 5) in the VD and vtD arms,

Table 2. Response rates

	VD, %	vtD, %	P*
After 2 cycles†			
CR (negative immunofixation)	6	4	.52
≥ nCR	16	16	1
≥ VGPR	21	24	.60
≥ PR	77	90	.01
After 4 cycles‡			
CR (negative immunofixation)	12	13	.74
≥ nCR	22	31	.15
≥ VGPR	36	49	.05
≥ PR	81	88	.19
After 1 course of melphalan 200 and ASCT§			
CR (negative immunofixation)	31	29	.77
≥ nCR	52	61	.20
≥ VGPR	58	74	.02
≥ PR	86	89	.54

*χ^2 test.
†Five and 3 patients had local and not centralized evaluations in the VD and vtD arms, respectively.
‡Two and 2 patients had local and not centralized evaluations in the VD and vtD arms, respectively.
§Eight and 2 patients had local and not centralized evaluations in the VD and vtD arms, respectively.

Table 3. Prognostic factors for CR + VGPR

	Treatment-adjusted odds ratio		
Variable	**Estimate**	**95% CI**	***P***
Chromosome 13 deletion			
No	1	—	.068
Yes	1.73	0.96-3.11	
β_2-microglobulin, mg/L			
≤ 3	1	—	.192
≥ 3	1.51	0.81-2.80	
≤ 3.5	1		.912
≥ 3.5	1.03	0.58-1.84	
≤ 6	1.87	0.85-4.12	.116
≥ 6	1		
t(4;14)			
No	1	—	.379
Yes	1.54	0.59-4.06	
del17p			
No	1.74	0.57-5.30	.328
Yes	1	—	
t(4;14) or del 17p			
No	1	—	.741
Yes	1.14	0.52-2.49	
International Staging System			
1	1	—	.323
2	1.18	0.61-2.30	
3	0.66	0.29-1.49	
Performance status			
0	1	—	.547
1	1.23	0.68-2.25	
2	1.69	0.42-6.81	
3 or 4	1.18	0.36-48.76	
Mobilization with cyclophosphamide			
No	1.46	0.62-3.45	.383
Yes	1	—	

— indicates not applicable.

respectively. Similarly, overall, a higher number of patients received maintenance therapy in the VD arm (n = 22 vs n = 15), which consisted of thalidomide 100 mg/day in 16 cases (vs 12 in the vtD arm) and lenalidomide 10 mg/day in 6 cases (vs 3 in the vtD arm). With a median follow-up time of 32 months, 45 of 99 and 53 of 100 patients had progressed in the VD and the vtD arms, respectively. Overall, there was no difference regarding progression-free survival between the 2 treatment arms (median, 30 months in the VD arm vs 26 months in the vtD arm, $P = .22$; Figure 2). Similarly, there was no difference regarding overall survival between the 2 arms of the trial.

Discussion

The goal of induction treatment before HDT/ASCT is to achieve the highest possible response rate while avoiding impairment of stem cell collection and significant toxicity that could preclude intensive therapy. VD is frequently considered the cornerstone of induction, and several triplet combinations have been developed based on this backbone, such as VD plus doxorubicin (PAD), VD plus cyclophosphamide (VCD), VD plus thalidomide (VTD), or VD plus lenalidomide (RVD).[16] Recently, VTD has been prospectively compared with TD,[12] and with VBMCP/VBAP/bortezomib,[13] and the efficacy results of these 2 studies, which are further discussed later in Discussion, are in favor of VTD. Until recently, no direct prospective comparison of VD versus VTD was available. Therefore, the aim of our study was to demonstrate the superiority of the VTD combination over VD as induction before HDT/ASCT and to show that a reduction in both bortezomib and thalidomide dosages, compared with previous applications of VTD, could translate into a reduction of the incidence of PN.

Considering the primary end point, the study failed to show a significant improvement in CR in the vtD arm. Nevertheless, the CR plus VGPR rate after 4 cycles was significantly increased in the vtD arm compared with the VD arm. Of note, the response rates achieved in the VD arm of the present study match those described in our previous induction trial comparing VAD with VD.[8] Several studies have already demonstrated that achievement of VGPR before ASCT is an important prognostic factor and is therefore a key objective, and that the choice of best induction therapy is of great importance.[2,3,5,16,17] Our vtD efficacy results are in line with those achieved in the prospective studies conducted by the Italian and the Spanish groups. In the Italian study (Gimema 26866138MMY3006), 3 cycles of VTD as induction were compared with 3 cycles of TD, and VGPR or better was achieved in 62% versus 28% of patients, respectively ($P < .0001$).[12] In the 3-arm randomized Spanish study (PETHEMA GEM05MENOS65), not yet reported as a full paper, 6 cycles of VTD as induction were compared with 6 cycles of TD, and with 4 cycles of VBMCP/VBAP followed by 2 cycles of bortezomib.[13] VTD yielded a 60% VGPR rate versus 29% in the TD arm and 36% in the third arm of the trial. In these 2 trials, bortezomib was given at 1.3 mg/m^2 on days 1, 4, 8, and 11 of each cycle, thalidomide was administered at 200 mg/day, and the incidence of grade 3 or 4 PN during induction was 10% in the Italian trial and 12% in the Spanish study. The toxicity results in our study are therefore of considerable interest. The reduced doses of bortezomib and thalidomide used in our trial led to a significant reduction in the rate of PN in the vtD arm compared with the VD arm; and although the number of induction cycles differs in each of the 3 trials, it seems that this incidence compares favorably with that observed in the 2 prospective studies using "full-dose" VTD as induction. In our study, 4 cycles of vtD were effective and manageable, and the number of patients who could not proceed to HDT was remarkably small (9%). Stem cell collection using G-CSF alone was slightly impaired compared with the VD arm, but subsequent mobilization using cyclophosphamide plus G-CSF and/or plerixafor was successful in almost all cases. In the Italian study, 90% (212 of 236) of the VTD patients could proceed to ASCT, but cyclophosphamide was systematically used to harvest stem cells. The course of ASCT in our study was uneventful, and no toxic death was reported, highlighting the

Table 4. Safety profiles of induction therapy with VD or vtD

	VD (n = 99)		vtD (n = 100)	
	Grades 1-4, %	**Grades 3 or 4, %**	**Grades 1-4, %**	**Grades 3 or 4, %**
Any adverse event	99	37	99	43
Hematologic toxicities				
Anemia	13	3	7	3
Neutropenia				
Thrombocytopenia	19	0	12	3
Infections	59	14	58	10
Herpes zoster	7	1	2	0
Thrombosis	4	1	7	2
Nonhematologic toxicities				
Cardiac disorders	9	1	12	2
Fatigue	53	2	46	6
Gastrointestinal symptoms	79	2	89	4
Peripheral neuropathy	70*	11†	53*	3†

*$P = .01$.
†$P = .03$.

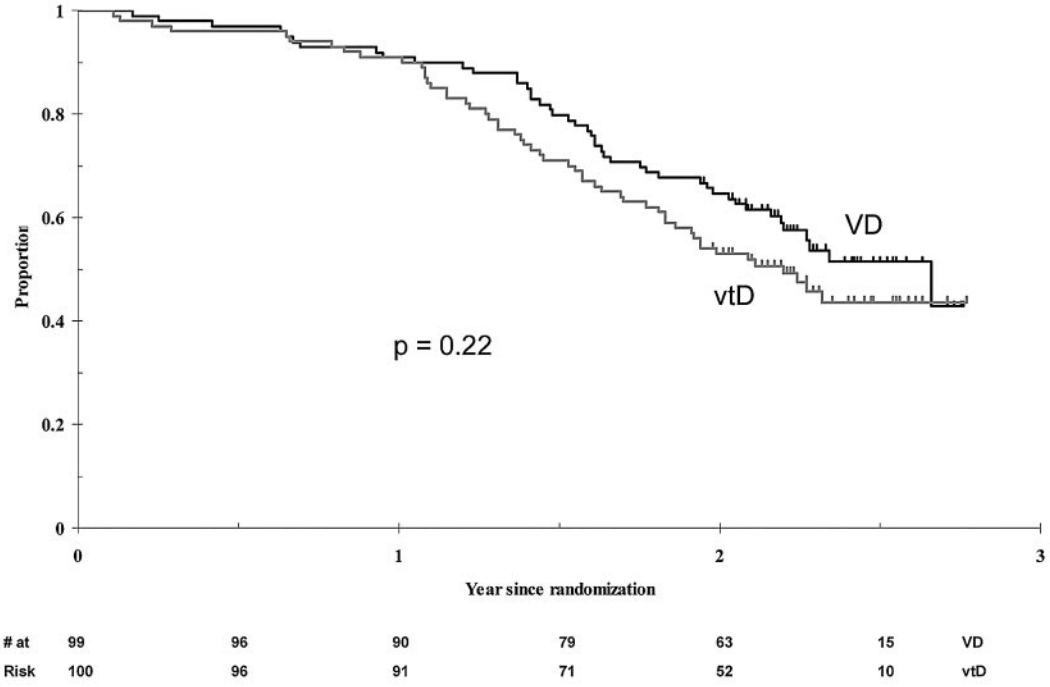

Figure 2. Progression-free survival.

feasibility of our approach. Our study was not designed to examine the impact of induction on progression-free survival because consolidation and maintenance treatments were not mandatory and not defined per protocol. The difference in response to induction observed between the 2 arms translated into a significant improvement in the rate of VGPR or better for the vtD arm after one course of high-dose melphalan, but the differences between treatment arms regarding the number of tandem ASCT procedures and the application of consolidation and maintenance therapies (more frequent in the VD arm) do not allow us to draw any conclusion on final outcome.

In conclusion, our study shows that vtD is a superior induction regimen compared with VD, with a higher response rate after induction translating into a greater CR plus VGPR rate after HDT, and with reduced toxicity regarding PN. Therefore, vtD, including reduced doses of bortezomib and thalidomide, can be considered as a new effective triplet combination before HDT/ASCT.

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Authorship

Contribution: P.M. and J.-L.H. designed the study and wrote the manuscript; H.A.-L. centrally analyzed blood and urine electrophoreses; P.M., J.-L.H., and H.A.-L. analyzed the data; and all authors served as investigators, contributed patient data, and approved the manuscript.

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