Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression

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ABSTRACT

Background

New treatment options offering enhanced activity in elderly, newly diagnosed patients with multiple myeloma are required. One strategy is to combine melphalan and prednisone with novel agents. We previously reported an 89% response rate, including 32% complete responses and 11% near complete responses, in our phase 1/2 study of bortezomib plus melphalan and prednisone (VMP) in 60 newly diagnosed multiple myeloma patients with a median age of 75 years. Here, we report updated time-to-events data and the impact of poor prognosis factors on outcome.

Design and Methods

Updated analyses of time to biochemical progression and overall survival with VMP were conducted, and compared with those of historical controls treated with melphalan and prednisone. A univariate analysis was performed to evaluate the influence of known prognostic factors on the time to progression.

Results

After a median follow-up of 26 months, the median time to progression with VMP was 27.2 months, compared with 20.0 months with melphalan plus prednisone. The median overall survival with VMP was not reached versus 26 months with melphalan and prednisone; the survival rate at 38 months was 85% versus 38%, respectively. Time to progression was not significantly affected by elevated β_2-microglobulin or lactate dehydrogenase levels, advanced age, or cytogenetic abnormalities, but was shorter in patients with albumin <3 g/dL, Karnofsky performance status ≤70%, bone marrow plasma cell infiltration ≥40%, and, particularly, high plasma cell proliferative activity (≥2.5% S-phase cells).

Conclusions

VMP is highly active and well tolerated in elderly patients with newly diagnosed muktiple myeloma, with 85% of patients alive at 3 years. Moreover, VMP may overcome the poor prognostic impact of various factors, particularly cytogenetic abnormalities.

Key words: multiple myeloma, bortezomib, melphalan, prednisone, elderly, clinical trial, first-line.

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Introduction

Melphalan plus prednisone (MP) is a standard of care for elderly newly diagnosed patients with multiple myeloma. However, its efficacy remains disappointing, with median progression-free survival and overall survival typically ranging between 17–21 months and 2–3 years, respectively.[1-3] New treatment options offering enhanced activity are required for this population of patients.

In order to improve outcomes in elderly patients with multiple myeloma, the combination of MP with novel agents that have marked activity in relapsed/refractory multiple myeloma has been investigated recently.[4-8] Thus, MP plus thalidomide has already demonstrated superiority versus MP.[5-7] We have previously reported that the proteasome inhibitor bortezomib may be combined successfully with MP (VMP regimen) in the treatment of elderly patients with newly diagnosed multiple myeloma, with a predictable and manageable safety profile.[4] The combination demonstrated substantial activity, with a response rate of 89%, including 32% complete responses and 11% near complete responses,[4] the highest complete/near complete response rate reported with MP-based regimens to date.[5-10] In addition, responses to VMP were not influenced by cytogenetic abnormalities. The response rate was higher than that among MP-treated historical controls, and 16-month progression-free survival, event-free survival, and overall survival rates were significantly greater with VMP than with MP.

Here, we report updated time to biochemical progression and overall survival data from our study of elderly subjects with multiple myeloma treated with VMP.

Design and Methods

Study design

The design of this phase 1/2, dose-escalation study, conducted at 19 centers in Spain for the PETHEMA Foundation, has already been reported.[4] Briefly, eligible patients were aged ≥65 years and had newly diagnosed, previously untreated, symptomatic multiple myeloma with measurable disease.[11] Patients received bortezomib 1.0 mg/m^2 (n=6) or 1.3 mg/m^2 (n=54) on days 1, 4, 8, 11, 22, 25, 29, and 32 for four 6-week cycles, and then on days 1, 8, 15, and 22 for five 5-week cycles. They also received oral melphalan 9 mg/m^2 and prednisone 60 mg/m^2 on days 1–4 of all nine cycles. The total maximum treatment duration was 49 weeks. Patients discontinued treatment if they had progressive disease, developed unacceptable toxicity, withdraw consent, or maintained a confirmed complete response for two cycles.[4] Disease response was assessed using European Group for Blood and Marrow Transplantation (EBMT) criteria[11] at the start of each cycle, at an end-of-treatment visit, and every 8 weeks for at least 6 months during the follow-up. Thereafter, patients were followed up every 3 months for survival.

This study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by the Institutional Review Board/Independent Ethics Committee at each participating center. All patients provided written informed consent before screening. Data were monitored by an independent/external contract research organization.

Assessments

Updated analyses of time to progression, event-free survival and overall survival in patients treated with VMP were conducted, and compared with historical control data from a similar population of patients treated with MP.[12] Time to alternative treatment (the time from inclusion in the study to initiation of an alternative myeloma therapy) was analyzed. To evaluate the influence of known myeloma prognostic factors on time to progression, a univariate analysis was conducted (log-rank for categorical variables, coded into categories with presumed better-to-worse prognosis). Variables included were: sex, age, M-protein class, International Staging System[13] stage, Karnofsky performance status, β2-microglobulin level, lactate dehydrogenase level, serum albumin, plasma-cell bone marrow infiltration, percentage of plasma cells in S-phase, and cytogenetic abnormalities detected by fluorescence *in situ* hybridization analysis.

Results

The patients' demographics and baseline characteristics have been reported previously; their median age was 75 years.[4]

Updated time-to-events data

All 60 patients received at least one dose of bortezomib, and were evaluable for time to progression and overall survival analyses. After a median follow-up of 26 months (range, 15–38 months), the median time to progression with VMP was 27.2 months, compared with 20.0 months among historical controls treated with MP (Figure 1A; p=0.001). The median event-free survival was 25.0 months, compared with 15.0 months among the historical controls p=0.001), and the event-free survival distribution curve (Figure 1B) was similar to that for time to progression. The median overall survival has not been reached with VMP, compared with 26 months with MP (Figure 1C; p<0.0001); the overall survival rate at 38 months is 85% with VMP versus 38% with MP (p<0.0001).

Among 25/60 (42%) patients receiving VMP who

have relapsed to date, 10/25 (40%) experienced biochemical but asymptomatic relapse. Of these ten patients, seven remain untreated, with a median follow-up from biochemical relapse of 5 months (range, 1–8 months). Consequently, the median time to alternative treatment has not been reached.

Influence of prognostic factors on time to progression

Table 1 shows the influence of the most important prognostic factors on median time to progression according to invariate analysis (the small sample size precluded the use of multivariate analysis). The median time to progression was significantly shorter in patients with albumin <3 g/dL, Karnofsky perfomance status ≤70%, bone marrow plasma-cell infiltration ≥40%, or, particularly, ≥2.5% plasma cells in the S-phase, compared with corresponding subgroups. It should be noted that these patients with a high proportion of S-phase plasma cells initially responded to VMP, but showed early disease progression with a markedly shorter time to progression (15 months). This finding has not been reported previously, and may contribute to our understanding of the mechanisms involved in secondary resistance to bortezomib.

By contrast, β2-microglobulin and lactate dehydrogenase levels, International Staging System stage, age, and cytogenetic abnormalities (Rb deletion/chromosome 13 deletion and IgH translocations such as t(4;14) and t(14;16)) did not significantly affect the median time to progression (Figure 1D and 1E). In six patients, chromosome 13 deletion and IgH translocations coexisted. This cytogenetic profile has been associated with a poor prognosis,[14] but the median time to progression with VMP in these six patients did not differ significantly from that of patients with normal cytogenetics (Figure 1E).

Table 1. Influence of prognostic factors on median time to progression among patients treated with VMP.

Factor	*n*	*Median TTP, months*	*p value*
Albumin			
≥3 g/dL	43	29	0.02
<3 g/dL	11	15	
Karnofsky performance status			
>70%	36	Not reached	0.004
≤70%	19	19	
Bone marrow plasma-cell infiltration			
<40%	33	Not reached	0.02
≥40%	24	24	
Plasma cells in S-phase			
<2.5%	27	Not reached	<0.0001
≥2.5%	10	15	
LDH level			
Normal	44	27	0.1
High	7	22	
β2-microglobulin level			
<3.5 mg/L	25	23	0.4
≥3.5 mg/L	29	29	
ISS Stage			
I/II	44	27	0.2
III	10	24	
Age			
75 years	36	27	0.3
>75 years	24	29	
Cytogenetic abnormalities			
No Rb del	20	Not reached	0.3
Rb del	13	25	
IgH –ve/no Rb del	23	29	0.3
IgH +ve/Rb del	6	23	

IgH, immunoglobulin heavy chain; ISS, International Staging System; TTP, time to progression; LDH, lactate dehydrogenase; Rb, retinoblastoma.

Safety

The VMP safety profile was unchanged from our previous report.[4] VMP was well tolerated in this elderly population of patients; toxicities were predictable and manageable.[4] The most common toxicities are listed in Table 2.

Discussion

These updated time-to-events results, following prolonged follow-up, from our phase 1/2 study of VMP in patients with newly diagnosed multiple myeloma represent extremely promising outcomes and confirm the substantial activity of VMP in terms of prolonged time to progression and overll survival in this elderly patient population. Indeed, the survival rate with VMP at 3 years is the highest reported to date with MP-based regimens.[5-10] These data indicate that, while until recently more than half of patients receiving MP therapy would have died by this time point, with VMP the majority (85%) of patients will be alive at 3 years. This is particularly notable considering the advanced age of the patients in this study (half were aged ≥75 years). However, it is important to note that the potential benefit on overall survival observed with VMP may also be partly due to differences in subsequent treatments that patients received at the time of the MP study and those currently used. In fact, fewer than 25% of the historical controls treated with MP received rescue therapy with novel agents.

The prolonged time to alternative therapy among patients who experienced biochemical but asymptomatic relapse represents the clinical benefit of VMP in elderly patients more effectively than the time to progression. Patients who remain off-treatment beyond biochemical relapse are spared from not only the return of their symptoms but also toxicities associated with commencing an alternative anti-myeloma treatment. The difference between the time to alternative treatment and the time to progression is of particular relevance in our study of VMP given the high number of patients achieving a complete response (immunofixation-negative for M-protein; 32%). In these patients, the time to progression may be adversely affected since a change to immunofixation-positive status (a bio-

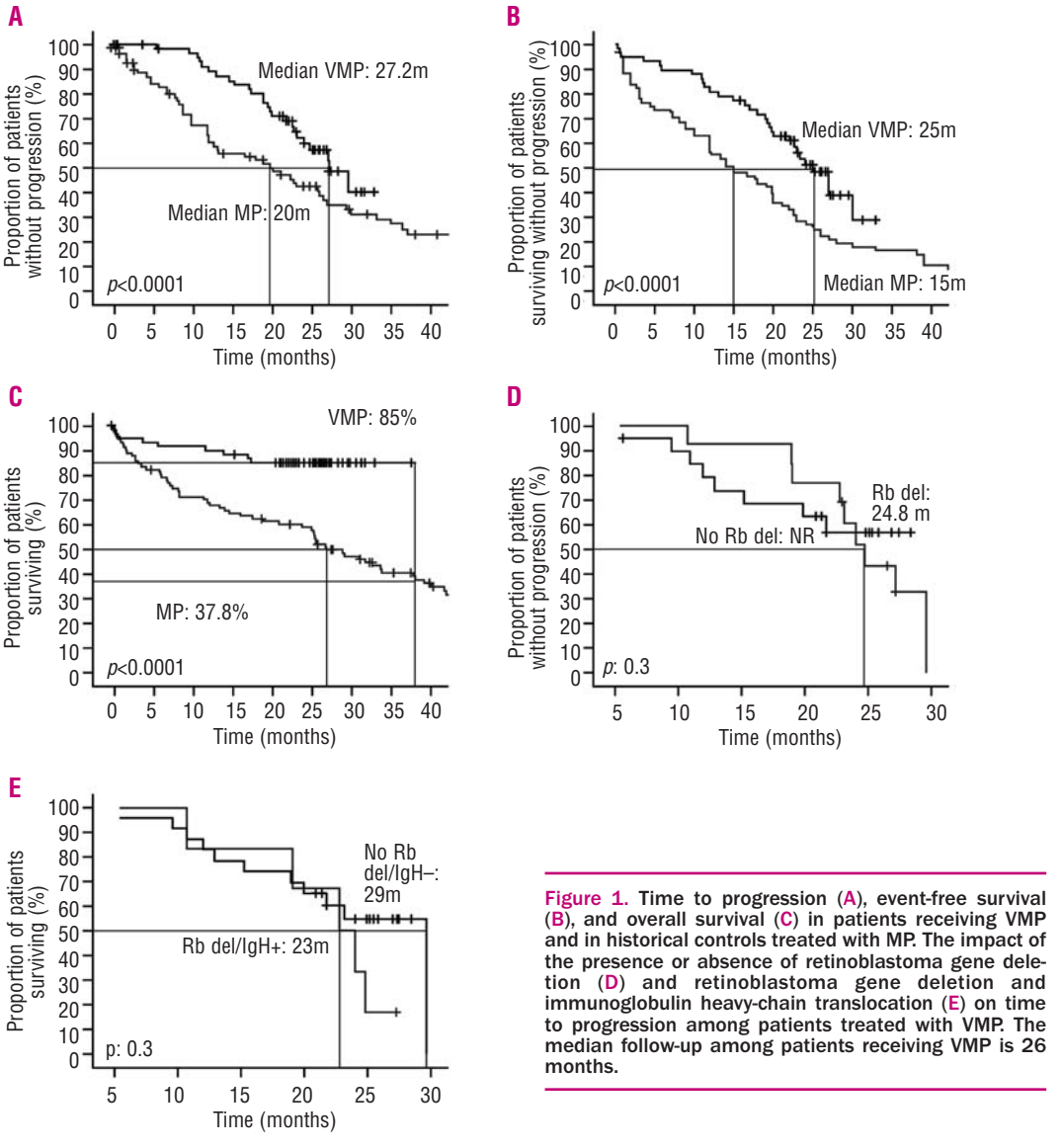

Figure 1. Time to progression (A), event-free survival (B), and overall survival (C) in patients receiving VMP and in historical controls treated with MP. The impact of the presence or absence of retinoblastoma gene deletion (D) and retinoblastoma gene deletion and immunoglobulin heavy-chain translocation (E) on time to progression among patients treated with VMP. The median follow-up among patients receiving VMP is 26 months.

chemical relapse) would count as an event in Kaplan-Meier analysis of time to progression, despite the absence of any other signs of disease activity. The possibility that the strict definition of relapse from complete response by EBMT criteria could lead to a paradoxically shorter remission duration in patients achieving a complete response than in those achieving a partial response was suggested by Bladé *et al*. when the criteria were first introduced.[11]

The findings from our univariate analysis of the impact of various prognostic factors on the median time to progression indicate that VMP may overcome the poor prognostic impact of factors such as advanced age,[15,16] increased lactate dehydrogenase[16] or β2-microglobulin[13] level, advanced International Staging System stage disease,[13] and, particularly, cytogenetic abnormalities (Rb deletion/chromosome 13 deletion[17,18] and IgH translocations).[19,20] This is the first prospective analysis to show that response and, more importantly,

Table 2. Most common (occurring in ≥30% of patients) adverse events in patients receiving VMP (n=60).

Adverse event	*Overall toxicities (%)*	
	All grades	*Grade 3/4*
Anemia	86	10
Thrombocytopenia	93	51
Infection	75	16
Neutropenia	85	43
Asthenia	63	5
Nausea	55	2
Diarrhea	55	16
Peripheral neuropathy	55	17
Constipation	52	8
Anorexia	38	2
Vomiting	30	2

time to progression are not influenced by cytogenetic abnormalities in patients treated with bortezomib-based regimens; in support of our findings, two recent retrospective reports have shown that response rate[21,22] and duration of response[22] to bortezomib in patients with relapsed and/or refractory multiple myeloma are independent of chromosome 13 deletion status determined by fluorescence *in situ* hybridization.

By contrast, other poor prognostic factors associated with high tumor burden and rapidly proliferating disease, such as low albumin,[13] poor Karnosky performance status, high degree of bone marrow infiltration,[23] and a high proportion of S-phase plasma cells,[24,25] appear to retain prognostic significance with VMP, as evidenced by statistically shorter median time to progression values. The highly significant association between a high proportion of S-phase plasma cells and a shorter median time to progression (15 months) is of particular relevance. This intriguing observation warrants further investigation to elucidate why patients with high tumor proliferative activity, although initially sensitive to bortezomib, soon become resistant.

In conclusion, VMP is highly active and well tolerated, and represents an attractive treatment strategy for patients aged ≥65 years with newly diagnosed multiple myeloma. VMP has recently been added as a treatment option for this population of patients in the US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Multiple Myeloma.[26] Results from the large international, randomized phase 3 VISTA (VELCADE as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone) trial of VMP compared with MP in patients aged ≥65 years who are not eligible for transplantation will further define the differences in efficacy and outcome between the regimens.

Authorship and Disclosures

M-VM, J-MH, JG-L, JBl, D-LE, HvdV and JFS-M declare potential conflicts of interest. M-VM, JG-L, JBl, and JFS-M have received honoraria; J-MH, JBl and JFS-M have received paid expert testimony within the past 2 years; M-VM, JG-L, JBl, and JFS-M disclose membership on another entity's Board of Directors or its advisory committees. Two of the authors (D-LE, and HvdV) are employed by companies (Millennium Pharmaceuticals, Inc, and Johnson & Johnson Pharmaceutical Research and Development, LLC, respectively) whose product [VELCADE (bortezomib)] was studied in the present work. HvdV has an ownership interest in Johnson & Johnson Pharmaceutical Research and Development, LLC. M-TH, N-CG, LP, MF, PG-S, J-JL, JdlR, M-JT, AS, JB, PR, FdA, AA, AO, DC, RG-S, FP and GM have no financial interests to declare.

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