Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase I/II study

Short title for running head: Bortezomib and MP in elderly untreated MM patients


From the Hematology Division, Grupo Español de MM (GEM/PETHEMA), Spain; Millennium Pharmaceuticals, Inc., Cambridge, MA, USA; and Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium.

Financial disclosure:
This study was sponsored by the PETHEMA Foundation, Spain, and supported by Millennium Pharmaceuticals, Inc and Johnson & Johnson Pharmaceutical Research & Development L.L.C.

*One of the authors (DLE) is employed by a company (Millennium Pharmaceuticals, Inc.) whose product (VELCADE, bortezomib) was studied in the present work.
*One of the authors (HvdV) is employed by a company (Johnson & Johnson Pharmaceutical Research & Development, L.L.C.) whose product (VELCADE, bortezomib) was studied in the present work.

Corresponding author:
Jesús-F San Miguel
Address: Paseo San Vicente 58-182; 37007 Salamanca, Spain
Tel: +34 923291384
Fax: +34 923294624
Email: sanmigiz@usal.es

Reprints:
Professor Jesús-F San Miguel, Paseo San Vicente 58-182; 37007 Salamanca, Spain
Word counts:
Abstract: 200
Text (excluding tables, figure legends, and references): 4,896 words
Figures and tables: 4 tables, 4 figures

Scientific section designation:
Clinical Trials and Observations

Key words:
multiple myeloma, bortezomib, melphalan, prednisone, elderly, clinical trial, IF-negative, first-line
ABSTRACT

Standard first-line treatment for elderly multiple myeloma (MM) patients ineligible for stem cell transplant is melphalan plus prednisone (MP). However, complete responses (CRs) are rare. Bortezomib is active in patients with relapsed MM, including elderly patients. This phase I/II trial in 60 untreated MM patients aged ≥65 years (half >75 years) aimed to determine dosing, safety, and efficacy of bortezomib plus MP (VMP). VMP response rate was 89%, including 32% immunofixation-negative CR, of whom half of those analyzed achieved immunophenotypic remission (no detectable plasma cells at $10^{-4}$–$10^{-5}$ sensitivity). VMP appeared to overcome the poor prognosis conferred by retinoblastoma gene deletion and IgH translocations. Results compare favorably with our historical control data for MP, notably response rate (89% vs 42%), event free survival at 16 months (83% vs 51%), and survival at 16 months (90% vs 62%). Side effects were predictable and manageable; principal toxicities were hematologic, gastrointestinal, and peripheral neuropathy, and were more evident during early cycles and in patients aged ≥75 years. In conclusion, in elderly patients ineligible for transplant, the combination of bortezomib plus MP appears significantly superior to MP, producing very high CR rates, including immunophenotypic CR, even in patients with poor prognostic features.
INTRODUCTION
For many years, the standard of care for patients with multiple myeloma (MM) has been melphalan plus prednisone (MP). Worldwide, MP is commonly used, with response rates of ~50%, although complete responses (CRs) are rare. Median duration of response is 1.5 years, median time to progression (TTP) is 18 months, and median overall survival (OS) is 2–3 years. The only treatment that has shown a significant survival advantage over conventional chemotherapy is high-dose therapy (HDT) supported by autologous stem cell transplantation (ASCT), which yields high CR or near CR (nCR) rates. In the Intergroupe Français du Myélome trial, 5-year survival rates were 52% with ASCT versus 12% with conventional chemotherapy. In the Medical Research Council Myeloma VII trial, median OS was 54 months versus 42 months, respectively. However, neither the Spanish (PETHEMA) myeloma trial nor the US Intergroup study demonstrated a significant difference in OS between ASCT and conventional chemotherapy after long-term follow-up.

HDT with ASCT is now considered standard therapy for younger patients. However, the elderly, patients in poor physical condition, and those with comorbidities are often not candidates for ASCT because of increased toxicity and reduced yield of CD34+ cells. Since approximately half of MM patients are aged > 70 years at diagnosis and therefore unlikely to be candidates for ASCT, there is an urgent need for more active and less toxic therapies for elderly patients. New treatments that produce high CR rates are needed, as CR is considered an important prognostic factor for survival. Recently, two randomized studies have shown significant benefits for the combination of MP plus thalidomide compared with MP, including higher CR rates, and longer TTP and OS.

Bortezomib (VELCADE®, Millennium Pharmaceuticals, Inc. and Johnson & Johnson Pharmaceuticals, Research and Development, L.L.C.) is the first proteasome inhibitor to enter the clinic. It is a reversible inhibitor of the 26S proteasome, an enzyme involved in the catabolic pathway for numerous intracellular regulatory proteins. Based on the results of two phase II trials and a randomized phase III trial, bortezomib has become a standard of care in relapsed MM.

Preclinical trials have demonstrated in vitro synergy when bortezomib is administered in combination with a wide range of cytotoxic agents, including melphalan. The combination of bortezomib and melphalan, administered at doses lower than their single-agent doses, was active and well tolerated in a phase I/II trial in relapsed and/or refractory MM. In the first-line setting, bortezomib monotherapy and bortezomib-based combinations have yielded high CR/nCR rates, of up to 29%, when given prior to ASCT. Despite extensive clinical
experience, there are no data from prospective trials evaluating bortezomib specifically in the elderly. A subgroup analysis of elderly patients (aged ≥ 65 years) in the phase III APEX trial in relapsed/refractory MM following 1–3 prior therapies showed that bortezomib was significantly more active than dexamethasone and was as well tolerated as in younger patients.40

Because the efficacy of both bortezomib and MP is well established, and both therapies are widely used in MM, it may be possible to improve response rate, and ultimately survival, by combining these therapies. The differing safety profiles of bortezomib and melphalan, and the tolerability of bortezomib in elderly patients, lend further support to their investigation in combination.

The primary objectives of this phase I/II study were to identify the most appropriate dose of bortezomib in combination with a standard MP treatment regimen (phase I), and to determine the efficacy of bortezomib plus MP (VMP) in terms of response rate (phase II). Secondary objectives were to: determine the safety and tolerability of VMP, assess efficacy in terms of OS, progression-free survival (PFS), and duration of response; and compare the efficacy of VMP with historical controls receiving MP alone.41 In addition, the study was designed to explore whether cytogenetic abnormalities, such as retinoblastoma (Rb) gene deletions and immunoglobulin heavy-chain (IgH) translocations, are predictive of response to VMP.

METHODS
Patient selection
Eligible patients were required to have the following: newly diagnosed symptomatic MM with measurable disease;42 be ≥ 65 years old; have Karnofsky Performance Status (KPS) ≥ 60% and life expectancy > 3 months. Patients were ineligible if they had previously received: any anti-MM treatment including bortezomib, investigational drugs within 14 days or major surgery within 4 weeks of enrollment. Patients were also ineligible if they were HIV positive or hepatitis–B-surface-antigen positive, or had active hepatitis C infection, myocardial infarction within 6 months of enrollment, or New York Heart Association class III or IV heart failure. Patients were excluded if, within 14 days prior to enrollment, they had a platelet count < 100 × 10^9/L; hemoglobin < 8 g/dL, absolute neutrophil count < 1.0 × 10^9/L, serum creatinine > 2 mg/dL, corrected serum calcium > 14 mg/dL, or grade ≥ 2 peripheral neuropathy.
**Study design**

This open-label, phase I/II, dose-escalation study was carried out at 19 centers in Spain for the PETHEMA Foundation. The 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. All patients provided written informed consent before screening. Data were monitored by an independent/external contract research organization.

**Treatment schedule**

Treatment comprised an initial phase consisting of four 6-week cycles of bortezomib 1.0 or 1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32, followed by a 10-day rest period, in combination with oral melphalan 9 mg/m² and oral prednisone 60 mg/m², both on days 1–4 (Figure 1). Each cycle was equivalent to two standard bortezomib monotherapy cycles.31 This was followed by a maintenance phase comprising five 5-week cycles of bortezomib 1.0 or 1.3 mg/m² on days 1, 8, 15, and 22, followed by a 13-day rest period, in combination with melphalan and prednisone as above (Figure 1).

**Phase I: identification of maximum tolerated dose (MTD)**

Bortezomib was to be administered at a dose of 1.0 mg/m² to the first cohort of six patients. If dose-limiting toxicities (DLTs) occurred in fewer than two of these patients, the next cohort of six patients was to receive a dose of 1.3 mg/m². By contrast, if DLTs occurred in two or more out of 6 patients or 4 or more out of 12 patients, the previous dose level (or bortezomib 0.7 mg/m² if DLTs occurred at the first dose level) would be identified as the MTD. Intrapatient dose escalation was not permitted. The starting dose of 1.0 mg/m² bortezomib was selected on the basis of a phase I dose-escalation trial of bortezomib plus melphalan.34,35

The following were defined as DLTs: grade 3/4 peripheral neuropathy persisting for > 3 weeks after discontinuation of bortezomib; any hematologic toxicity of grade 4 intensity or preventing administration of 3 or more of the 8 bortezomib doses of the first treatment cycle; grade 3/4 febrile neutropenia; grade 3/4 gastrointestinal toxicities (except for grade 3 nausea/vomiting if the patient had not received adequate antiemetic prophylaxis); and any other grade 3/4 nonhematologic toxicity considered related to VMP by the principal investigator. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology for Adverse Events (NCI CTC, Version 3.0). MTD determination was based on occurrence of DLTs during the first induction treatment cycle only.
Phase II: expanded cohort

After identification of the MTD, it was planned for the dose level to be expanded to include up to a total of 60 patients at MTD for the phase II part of the study. A full treatment course was the same as for phase I and is outlined in Figure 1. Treatment beyond 49 weeks was not permitted. Patients maintaining a confirmed CR for 2 treatment cycles beyond CR confirmation (minimum 10 weeks) were withdrawn from the study, as were patients who developed progressive disease (PD), experienced unacceptable toxicity, or withdrew consent.

Dose modifications

In patients with any grade 4 hematologic toxicity observed on day 43 of the 6-week cycle or day 36 of a 5-week cycle that was considered by the investigator to be study drug-related, the cycle was delayed for up to 2 weeks until resolution to baseline or \( \leq \) grade 1. In patients with \( \geq \) grade 3 nonhematologic toxicity that was considered by the investigator to be study-drug related, chemotherapy was held until resolution to baseline or \( \leq \) grade 1. Standard bortezomib dose reduction was applied in patients experiencing neuropathic pain and/or peripheral sensory neuropathy. During the phase II part of the study, the bortezomib dose was reduced (from 1.3 to 1.0 mg/m\(^2\) or from 1.0 to 0.7 mg/m\(^2\)) if 3 or more of the 8 bortezomib doses in any of the 6-week cycles had to be missed. If patients developed any grade 4 hematologic toxicity during week 3 or 6 of the 6-week cycles, the melphalan dose was reduced by 25% for the subsequent cycle. If patients developed renal insufficiency (creatinine \( \geq \) 2 mg/dL), the melphalan dose was reduced by 50%; patients were withdrawn if creatinine was > 4 mg/dL. Up to two dose reductions of melphalan or bortezomib were permitted for each drug. Prednisone dose reductions were permitted for grade 3 or 4 corticosteroid toxicities.

Concomitant medications

All patients received intravenous bisphosphonates every 4 weeks during the study. Supportive therapy for MM (e.g. erythropoietin, G-CSF, platelet or red blood cell transfusions) was allowed.

Study assessments

Screening tests carried out \( \leq \) 14 days before study start included medical history, physical examination, hematology, clinical chemistries, posteroanterior and lateral chest X-rays, electrocardiogram, bone scans and bone marrow aspiration for morphology, flow cytometry
(including S-phase analysis), and cytogenetic studies. Blood and 24-hour urine samples for quantitation of M-protein and immunoglobulins, and assessment of M-protein by immunofixation (IF) in serum, were collected from all patients.

Disease response was assessed according to the European Group for Blood and Marrow Transplantation criteria at the beginning of each treatment cycle (every 6 weeks during initial treatment and every 5 weeks during maintenance treatment), at the end-of-treatment visit, and at follow-up visits. In patients with secretory MM, blood and urine samples were collected at the start of each treatment cycle for quantitative M-protein, immunoglobulin quantitation, and assessment of M-protein by IF. KPS, and clinical chemistry were assessed at the start of each treatment cycle. Hematologic parameters were assessed on bortezomib dosing days. All AEs (graded according to NCI CTC version 3.0) and use of concomitant medications and supportive therapies were recorded. All efficacy and safety assessments, including bone marrow analyses and skeletal surveys, were repeated at the end-of-treatment visit.

After completing treatment, all patients were monitored for response every 8 weeks for at least 6 months (follow-up period) and every 3 months thereafter for survival.

**Minimal residual disease (MRD) analysis by flow cytometry (FC)**

As previously described, myelomatous plasma cells (PC) can be unequivocally distinguished from normal plasma cells on the basis of aberrant expression of CD19, CD28, CD38, CD56, CD45, and CD117. This allows for the quantitation of residual myelomatous PC following treatment. For this purpose we used a two-step procedure in which up to 2x10^6 cells were acquired through a specific 'live-gate' drawn on SSC/CD38^{strong+ve}/CD138^{+ve} dot-plot. A multiparametric analysis of antigenic expression was performed using Paint-A-Gate PRO software (Becton Dickinson, San Jose, CA). The sensitivity of this technique ranges between 10^{-4} and 10^{-5}, i.e. identification of one residual PC among 10,000 to 100,000 normal cells. PC DNA ploidy status and cell cycle were analyzed as previously described using a double staining procedure for nuclear DNA (with propidium iodide) and surface PC antigen (CD38 and CD138).

**Fluorescence *in situ* hybridization (FISH) analysis**

Interphase FISH studies for the detection of IgH translocations were performed using LSI *IGH* Dual Color, break apart rearrangement probe (Vysis, Downers Grove, IL). Patients with IgH translocations were analyzed for 11q13 partner (LSI IgH /CCND1, dual fusion translocation probe, Vysis), for 4p16 (BAC clones L75b9, L184d6, L190b4, L96a2; VH:
cosmid and IgH6-9/CH: B158 A2) and for 16q23 (BAC clones 356D21, 484H2, 10205 and 10206, kindly provided by R. Fonseca). The presence of 13q and 17p deletion was evaluated with a specific probe for RB LSI 13 (RB1) and P53 -LSI P53 (17p13.1).45

**Statistical analysis**

A population of 60 patients provided 80% power to detect ≥ 50% response rate (CR + PR) with VMP versus 40% in historical controls receiving MP, tested at a two-sided α-level of 0.05.

The efficacy population (TTP, event-free survival [EFS] and OS) included all treated patients who received at least 1 dose of bortezomib per protocol. Patients who received at least 1 cycle of bortezomib were evaluable for response. Patients with a partial response (PR) were subdivided to show those with an nCR, defined as negative electrophoresis but IF-positive.

The secondary efficacy analysis was to determine whether VMP provided benefit over historical data for MP in a similar patient population in terms of response rate, PFS, and OS. Time-related endpoints were analyzed using the Kaplan–Meier method, adjusted for stratification factors (age, Karnofsky performance status, albumin, lactate dehydrogenase [LDH], C-reactive protein, β2-microglobulin, and bone marrow infiltration), and tested for a treatment difference versus the historical data using log-rank tests (two-sided, α = 0.05). Exploratory analyses were conducted to investigate whether potential prognostic variables, used as covariates in logistic regression (response rate), substantially affected the study conclusions.

TTP was calculated from the time of inclusion until the date of disease progression, with deaths due to causes other than progression not counted as an event but censored at that time-point. EFS was calculated from the time of inclusion until the date of progression, relapse, death for any cause or the date the patient was last known to be in remission. OS was calculated from the time of inclusion until the date of death for any cause or the date the patient was last known to be alive.

The historical control group consisted of 96 patients treated with MP. These correspond to patients in a randomized trial of MP versus melphalan plus dexamethasone (MD) recently reported by our group.41

The safety population included all patients who received at least one dose of bortezomib. Safety analyses were conducted based on incidence, intensity, and type of AE, and clinically
significant changes in patients’ physical examination findings, vital signs, and clinical laboratory results. All data were monitored by an independent/external contract research organization.

RESULTS

Patient demographics and disposition
Between January 2004 and April 2005, 12 patients were enrolled in phase I (6 at bortezomib 1.0 mg/m² and 6 at 1.3 mg/m²) and 48 patients in phase II (all at 1.3 mg/m²), giving a total of 60 patients for evaluation. Almost half of the patients were aged > 75 years. Demographic and baseline characteristics, summarized in Table 1, were similar to the MP historical controls.41

All 60 patients received at least one dose of study drug; 7 failed to complete the first cycle of VMP (withdrawal of consent and early death each in 3 patients, and diagnosis of lung cancer during the fourth week of the first cycle in 1 patient) and were therefore not evaluable for response. Nevertheless, all 60 patients received 1 dose and were evaluable for TTP, EFS, and OS, as well as safety.

Identification of MTD
No DLTs occurred during phase I. Two patients experienced grade 3 neutropenia and one developed grade 3 thrombocytopenia, none of which were DLTs. Therefore the 1.3 mg/m² bortezomib dose level was expanded for phase II.

Exposure to study drug
Delivery of planned doses was as follows: 37% of patients received all doses of bortezomib; 43% missed 2–4 doses, and 20% missed 5 or more doses. Mean duration of treatment was 7.5 months; to date, 79% of patients have completed at least the first 4 cycles of therapy and 62% have received all planned cycles. The median number of cycles administered was 7 (range 2–9), a duration of more than 9 months.

Efficacy
In the 53 patients who completed at least the first cycle, the response rate (CR + PR) was 89%, including 32% IF-negative CR and 11% nCR (Table 2). Responses were rapid: response rate after the first cycle (6 weeks) was 70%, including 6% IF-negative CR. Median time to response was 2.7 months (range: 1–10 months). The best response occurred within the first 3 cycles (18 weeks) in 74% of patients (Figure 2). Of 37 patients who completed scheduled treatment, 35% achieved CR, 11% nCR, and 46% PR for an overall 92%
response rate. The patients who achieved CR underwent a median of 5 cycles of therapy (range 3–8). Of 16 patients who discontinued treatment prematurely but were evaluable for response, 25% (n = 4) achieved CR, 12.5% nCR (n = 2) and 44% PR (n = 7), for an overall 81.5% response rate, similar to the total population. Notably, the response rate after just 1 cycle of VMP was higher than in the historical controls after 6 cycles of MP (42% response rate; 3% nCR, 39% PR) (Table 2).

After a median follow-up of 16 months (range: 11–24 months), median TTP has not been reached. At 16 months, 91% of patients were free of disease progression, and EFS rate was 83%. Six of the eleven events were disease progression, and four of these six patients are still alive. The projected overall 2-year survival rate is 86%. Median OS has not been reached. As shown in Figure 3, these results compare favorably with PFS, EFS, and OS in our MP historical control (at 16 months, PFS: 91% vs 66% ($P = .002$), EFS rate: 83% vs 51% ($P = .0003$), OS rate: 90% vs 62% ($P = .0012$)).

Among 17 patients achieving IF-negative CR, we assessed minimal residual disease in 12 using multiparametric flow cytometry. In 6 of these patients, no malignant plasma cells were detectable with a sensitivity level of $10^{-4}$ to $10^{-5}$, representing immunophenotypic remission. Exploratory logistic regression analyses demonstrated that none of the potential risk factors investigated (age > 75 years; albumin < 3.5 g/dL; LDH > 460 mg/dL, C-reactive protein > 4 mg/L; $\beta_2$-microglobulin $\geq$ 3.5 mg/L; bone marrow infiltration $\geq$ 50%) was predictive of IF-negative CR. Further analyses using the same risk factors to compare patients with CR or PR (n = 47) versus those with stable disease (n = 6) demonstrated that only bone marrow infiltration $\geq$ 50% was significantly associated with lack of response ($P = 0.05$).

Cytogenetic information by FISH was available in 33 patients. To determine whether Rb gene deletion predicted response to VMP, we compared response rate among patients with (n = 13) and without (n = 20) Rb deletion. All patients with Rb deletion responded (Table 3). The response rate among patients with (n = 8) and without (n = 20) IgH translocations was almost identical (88% vs 82%, Table 3). Although the numbers are small, CR/nCRs were observed not only in patients with t(11;14) (one out of two), but also in patients with t(4;14) and t(14;16) (one out of three, respectively). PFS and EFS among patients with Rb deletion or IgH translocation were similar to those of patients without these cytogenetic alterations (Figure 4) and similar to those of the overall population. Finally, DNA ploidy status was analyzed in 35 patients; among 23 hyperdiploid and 12 diploid patients, the response rates were 87% (36% CR) and 100% (47% CR), respectively.
Safety

As previously mentioned, of the 60 patients included in the study, 7 failed to complete the first cycle (early death in 3, withdrawal of informed consent in 3, and 1 diagnosis of lung cancer); 37 patients (62%) completed treatment (24 received all planned cycles and 13 achieved early CR and therefore stopped therapy after a median of 5 cycles [range 3–8]). The remaining 16 patients discontinued treatment due to the following reasons: withdrawal of consent in 3 patients (in cycles 2, 4, and 7); and AEs in 13 patients (peripheral neuropathy in 6 patients; severe infection, septic shock, grade 3 diarrhea, and sustained grade 4 thrombocytopenia that was possibly immune thrombocytopenic purpura each in 1 patient, and disease progression in 3 patients).

The most common AEs in the 60 safety-evaluable patients are shown in Table 4. The most common grade 3/4 AEs included hematologic toxicity (thrombocytopenia [51%] and neutropenia [43%]), peripheral neuropathy (17%), and diarrhea (16%). Despite the high rate of hematologic toxicity, the frequency of grade 3/4 infection was low (16%). Notably, the overall incidence of Herpes zoster infection was 13% in the first 38 patients. Subsequently, the protocol was amended to recommend prophylactic acyclovir. After this, only 2/30 patients who followed protocol developed Herpes zoster infection. Sixteen (27%) patients received G-CSF support. The majority of AEs occurred during the first 2 treatment cycles (Table 4).

Bortezomib dose was reduced in 14 (23%) patients and interrupted in 8 (13%). Among patients whose bortezomib dose was reduced, 10 required a single reduction to 1.0 mg/m² (peripheral neuropathy in 5 patients, hematologic toxicity in 3 patients, nonhematologic toxicity in 2 patients) and 4 required a further reduction to 0.7 mg/m², all for peripheral neuropathy. A further 2 patients required melphalan dose reductions to 6.75 mg/m² for hematologic toxicity.

Seven (12%) patients died during study treatment. Of these, 4 were early deaths (during the first 6 weeks of treatment) in patients aged > 75 years, due to: pulmonary thromboembolism; septic shock with grade 3 neutropenia; pulmonary hypertension with right ventricular insufficiency; and lung cancer diagnosed during the fourth week of the first cycle. The remaining 3 deaths were from disease progression in 2 patients and septic shock in the third, who achieved CR and died after the third cycle of therapy. None of the deaths was considered related to any of the study drugs.
DISCUSSION

Our study aimed to determine the recommended dose of bortezomib in combination with oral MP in elderly MM patients ineligible for ASCT, and to investigate the efficacy and safety of VMP. The baseline characteristics of patients included in the present study appear to be broadly representative of this patient population. The inclusion of elderly patients is of particular interest: almost half of the study population was aged > 75 years and 17% were > 80 years old. No patients in the dose-escalation phase of the study experienced DLTs, and therefore we used a bortezomib dose of 1.3 mg/m² to further evaluate VMP. Our results demonstrate that in elderly untreated patients with MM who are not suitable for transplant, VMP is highly active and well tolerated. The 32% IF-negative CR rate observed with VMP is noteworthy, as IF-negative CR is considered an important predictor for survival.7,43,46-51 Moreover, response was of high quality, as demonstrated by multiparametric flow cytometry, and responses were independent of cytogenetic abnormalities.

Consequently, VMP represents an attractive option for elderly patients, for whom new treatment strategies are clearly needed. In this setting, encouraging results have recently been reported for the combination of thalidomide plus MP (MPT) in newly diagnosed elderly MM patients.22,23,52 An Italian randomized study demonstrated significant benefit with MPT compared with MP, with a response rate of 76% (16% CR, 12% nCR) for the MPT arm versus 48% (2% CR, 5% nCR) for MP. This was associated with a higher EFS rate (54% vs 27% at 2 years) and OS rate (80% vs 64% at 3 years).22 Similarly, the Intergroupe Français du Myélome group has reported benefits in terms of median PFS (28 vs 17 months) and median OS (not reached at 55 months vs 30 months) of MPT compared with MP in a randomized study.23

Results from the present study compare favorably with our MP historical control data. After only 1 cycle of VMP we obtained a higher response rate (70%, including 6% CR, 2% nCR, 62% PR) than with 6 cycles of MP in the historical controls (42%, including 3% nCR, 39% PR). Furthermore, the proportion of CRs increased with additional treatment cycles up to 32% CR plus 11% nCR in the current study. Moreover, VMP yielded a longer EFS (at 16 months, 83% vs 51%) and OS (at 16 months, 90% vs 62%) than our MP historical control data.

Another notable finding of the present study was the pattern of response to VMP. Although responses occurred rapidly, quality of responses (IF-negative CR) improved with subsequent cycles. This observation is consistent with results from the recent update of the large international phase III study of bortezomib (APEX) in which it was seen that, despite rapid
initial response, best response to single-agent bortezomib as measured by M-protein reduction continues to improve over the treatment course, with approximately 20% of patients achieving maximum M-protein reduction in eight 3-week cycles or later. The slow but continuous activity of melphalan could also play a role in the improved response over time. In the present study, patients maintaining a CR for 2 treatment cycles after confirmed CR discontinued treatment. Therefore, it is possible that in some responding patients, a substantially shorter course of treatment may be possible when bortezomib is added to MP, although this has not been evaluated prospectively.

None of the potential factors evaluated in the present study, including cytogenetic abnormalities, was found to predict response to VMP therapy. A 100% response rate was seen in 13 patients with Rb deletion, which is an independent prognostic factor for shorter survival and poor response to conventional chemotherapy and tandem transplants. A similar pattern was seen with IgH translocations, including t(4;14) and t(14:16), which are also predictive of poor prognosis. It is possible that the unique mechanism of action of bortezomib overcomes the influence of these adverse prognostic factors; this is consistent with the results of a recent analysis of the APEX trial, in which bortezomib appeared to overcome the adverse impact of del(13) on response rate. In addition, our study shows no influence of cytogenetic abnormalities on the PFS and EFS of patients treated with VMP.

VMP was well tolerated, and toxicities were predictable and manageable. Thirteen (21%) patients discontinued from the study because of unacceptable toxicity; in most cases, AEs could be managed by dose modification. The frequency and severity of asthenia, rash, and gastrointestinal side effects was similar to that observed in the APEX, SUMMIT, and CREST studies. However, we observed higher incidences of hematologic toxicity and peripheral neuropathy. The former can be clearly related to the safety profile of melphalan, leading to a higher incidence of hematologic AEs than in other trials of bortezomib as first-line therapy. Melphalan is typically associated with a relatively high incidence of neutropenia and thrombocytopenia. Therefore the incidence of thrombocytopenia in this trial was not unexpected and is consistent with the known side effects of melphalan. Nevertheless, it should be emphasized that in the present study patients were evaluated twice a week, while in studies of MP or MPT, patients were only assessed every 4–6 weeks; this less frequent reporting may underestimate the incidence of side effects, particularly hematologic toxicity, which is generally only detected through cell counts. Overall toxicity was higher in patients aged ≥ 75 years, in particular anemia, infection, neutropenia, asthenia, and peripheral neuropathy. This could be related to the physical condition of these elderly patients.
Peripheral neuropathy occurred in half of the patients in the present study and was of grade 3/4 intensity in 17%. This figure is higher than in the APEX trial and could be related to the advanced age of patients in the current study. Consistent with this hypothesis, the incidence of grade 3 peripheral neuropathy in patients aged ≥ 75 years was much higher than in those aged < 75 years. The presence of peripheral neuropathy at diagnosis is often underestimated in MM patients, better recognition of underlying peripheral neuropathy may facilitate prompt dose reductions when mild symptoms develop in this fragile population of patients.

Of concern was the potential for cumulative toxicity with additional cycles of VMP. Our results do not support such a hypothesis: indeed, the frequency of side effects decreased after cycle 3. Again, this may be related to the physical condition of elderly patients, since it is well known that major toxicities, including deaths, are particularly common within the first two months with increased tumor burden. Additionally, the rapid responses obtained with VMP may have contributed to the subsequent decrease in side effects. Interestingly, only 4 (7%) early deaths occurred in this study, which is similar in frequency to that we previously observed with MP (8%) or melphalan plus dexamethasone (14%) in similar patient populations. Among 3,107 MM patients treated in Medical Research Council trials between 1980 and 2002, 299 (10%) died within 60 days of trial entry, again illustrating that the early death rate in the present study is comparable with that seen in studies of conventional agents.

Our study demonstrates that VMP is a highly active regimen for newly diagnosed patients with MM aged ≥ 65 years who are not candidates for ASCT. The CR/nCR rate was 43%; most of these were IF-negative CRs (32%) and half of the IF-negative CR patients who were analyzed achieved immunophenotypic remission. On the basis of these promising results, VMP is being compared with MP in an international, phase III randomized trial (VISTA) in patients ≥ 65 years old not suitable for transplantation. In conclusion, VMP is a more effective first-line regimen than MP in patients not eligible for transplant, offering new hope to these difficult-to-treat patients.
REFERENCES


## TABLES

### Table 1. Patient demographics and baseline characteristics.

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<th>VMP (n = 60)</th>
<th>Historical MP (n = 96)</th>
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<td>IgA</td>
<td>34</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>Bence-Jones (BJ)</td>
<td>7</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Stage (ISS) (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>29</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>II</td>
<td>54</td>
<td>54</td>
<td>NS</td>
</tr>
<tr>
<td>III</td>
<td>17</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td><strong>KPS (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 70</td>
<td>20</td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>80</td>
<td>47</td>
<td>38</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 90</td>
<td>32</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Median (range)</strong></td>
<td></td>
<td>80 (60–100)</td>
<td></td>
</tr>
<tr>
<td>Albumin &lt; 3.5 g/dL (%)</td>
<td>20</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>C-reactive protein &gt; 4 mg/L (%)</td>
<td>20</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>LDH &gt; 460 mg/dL (%)</td>
<td>16</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>β₂ microglobulin ≥ 3.5 mg/L (%)</td>
<td>54</td>
<td>39</td>
<td>NS</td>
</tr>
<tr>
<td>Bone marrow infiltration ≥ 50% (%)</td>
<td>35</td>
<td>27</td>
<td>NS</td>
</tr>
</tbody>
</table>

ISS indicates International Staging System; KPS, Karnofsky Performance Status; LDH, lactate dehydrogenase; NS, not significant (P > .05); VMP, bortezomib plus melphalan plus prednisone.

*Using Chi-squared test and Fisher’s exact test.
Table 2. Response rates after 1 cycle of bortezomib plus melphalan plus prednisone (VMP), best response after a median of 7 cycles of VMP, or 6 or 12 cycles of melphalan plus prednisone (MP) (historical control data)

<table>
<thead>
<tr>
<th></th>
<th>VMP (n = 53), first cycle</th>
<th>VMP (n = 53), best response after a median of 7 cycles</th>
<th>Historical MP (n = 87), best response after 6 cycles* 41</th>
<th>Historical MP (n = 77), best response after 12 cycles* 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (%)</td>
<td>70</td>
<td>89</td>
<td>42</td>
<td>35</td>
</tr>
<tr>
<td>CR IF-negative</td>
<td>6</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR IF-positive</td>
<td>2</td>
<td>11</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>PR</td>
<td>62</td>
<td>45</td>
<td>39</td>
<td>26</td>
</tr>
<tr>
<td>Minor response</td>
<td>6</td>
<td>0</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>Stable disease</td>
<td>24</td>
<td>11</td>
<td>31†</td>
<td></td>
</tr>
</tbody>
</table>

CR indicates complete response; IF, immunofixation; PR, partial response.

*Cycles were 4 weeks in duration; MP administered at the same dose as in the VMP regimen.

†Or progressive disease.
Table 3. Response rates (%) among subgroups of patients according to retinoblastoma (Rb) deletion and immunoglobulin heavy-chain (IgH) translocations, determined by fluorescence in situ hybridization (patients treated at bortezomib 1.3 mg/m² dose level)

<table>
<thead>
<tr>
<th></th>
<th>Rb deletion (n = 13)</th>
<th>No Rb deletion (n = 20)</th>
<th>IgH (n = 8)</th>
<th>No IgH (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR IF-negative</td>
<td>100*</td>
<td>66</td>
<td>88†</td>
<td>82</td>
</tr>
<tr>
<td>CR IF-positive</td>
<td>42</td>
<td>30</td>
<td>25</td>
<td>41</td>
</tr>
<tr>
<td>PR</td>
<td>15</td>
<td>5</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Stable disease</td>
<td>46</td>
<td>35</td>
<td>50</td>
<td>36</td>
</tr>
</tbody>
</table>

CR indicates complete response; IF, immunofixation; PR, partial response.

*P = .16 vs no Rb deletion.
†P = .7 vs no IgH translocation.
Table 4. Most common (occurring in ≥ 30% of patients) adverse events (AEs) (n = 60), and comparison of rates of grade 3/4 AEs in the first 2 cycles versus in the third cycle onwards, and in patients aged < 75 years versus in patients aged ≥ 75 years.

<table>
<thead>
<tr>
<th>AE</th>
<th>Overall toxicities (%)</th>
<th>Grade 3/4 AEs by treatment cycle (%)</th>
<th>Grade 3/4 AEs by patient age (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3/4</td>
<td>1st and 2nd cycles</td>
</tr>
<tr>
<td>Anemia</td>
<td>86</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>93</td>
<td>51</td>
<td>33</td>
</tr>
<tr>
<td>Infection</td>
<td>75</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>85</td>
<td>43</td>
<td>33</td>
</tr>
<tr>
<td>Asthenia</td>
<td>63</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>55</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>55</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>55</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>52</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Anorexia</td>
<td>38</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS

Figure 1. The VMP schedule was based on the standard bortezomib monotherapy dosing schedule. The treatment consisted of four 6-week cycles followed by the maintenance phase consisting of five 5-week cycles, giving a total of 49 weeks of treatment.

Figure 2. Response to VMP was rapid. The percentage of responding patients achieving their best response to VMP is shown: (A) by treatment cycle, and (B) over time.

Figure 3. Time to events data in patients receiving VMP. (A) Progression-free survival, (B) event-free survival, and (C) overall survival of patients receiving VMP versus MP historical controls. The 16-month time point has been highlighted as it represents the median follow-up in patients treated with VMP.

Figure 4. Influence of cytogenetic abnormalities on progression-free survival and event-free survival. The graphs demonstrate the effect of (A) retinoblastoma gene deletion (Rb del) and (B) IgH translocations (IgH tr) on progression-free survival and event-free survival. NS indicates not significant ($P > .05$).
Figure 1

Four 8-week cycles

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>8</th>
<th>11</th>
<th>22</th>
<th>25</th>
<th>29</th>
<th>32</th>
<th>33-42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rest Period</td>
</tr>
<tr>
<td>Melphalan 9 mg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone 60 mg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Five 8-week cycles

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>8</th>
<th>15</th>
<th>22-25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rest Period</td>
<td></td>
</tr>
<tr>
<td>Melphalan 9 mg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone 60 mg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total = 49 weeks of treatment
Figure 2

A

Proportion of patients achieving best response in each cycle

Treatment cycle

74%

B

Proportion of patients achieving best response (%)

Time (months)
Figure 4
Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase I/II study

Maria-Victoria Mateos, Jose-M Hernandez, Miguel-T Hernandez, Norma-C Gutierrez, Luis Palomera, Marta Fuertes, Joaquin Diaz-Mediavilla, Juan-J Lahuerta, Javier de la Rubia, Maria-Jose Terol, Ana Sureda, Joan Bargay, Paz Ribas, Felipe de Arriba, Adrian Alegre, Albert Oriol, Dolores Carrera, Jose Garcia-Larana, Ramon Garcia-Sanz, Joan Blade, Felipe Prosper, Gemma Mateo, Dixie-Lee Esseltine, Helgi van de Velde and Jesus-F San Miguel

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