Bendamustine, bortezomib and prednisone for the treatment of patients with newly diagnosed multiple myeloma: results of a prospective phase 2 Spanish/PETHEMA trial

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ABSTRACT

Bendamustine is a bifunctional alkylating agent with proven activity in myeloma. In this study 60 newly diagnosed myeloma patients were given bendamustine plus bortezomib and prednisone in a regimen consisting of one cycle of bortezomib twice weekly for 6 weeks (1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32), plus bendamustine (90 mg/m^2 on days 1 and 4) and prednisone. The following cycles included bortezomib once weekly. Patients who were transplant candidates proceeded to stem cell collection after four cycles and the transplant was performed after six cycles. Patients who were not candidates for transplantation received up to nine cycles. Forty-two patients were transplant candidates and after six cycles, 50% achieved at least a very good partial response, with 24% having complete responses; 35 proceeded to a transplant, and the complete response rate was 54%. Seventeen patients continued up to nine cycles, and 57% achieved at least a very good partial response, including 26% with complete responses. The 2-year progression-free survival and overall survival rates were 62% and 86%, respectively. The safety profile was manageable, but stem cell mobilization was compromised in 35% of patients. In summary, this combination is effective in untreated patients, with an acceptable toxicity profile, but given the introduction of second-generation novel agents and monoclonal antibodies, the combination will probably be better reserved for relapsing patients, in whom stem cell collection is not needed, while cost-effective combinations with non-cross-resistant drugs continue to represent a medical need. *This trial was registered with ClinicalTrials.gov, number NCT01376401.*

Introduction

Multiple myeloma (MM) is a neoplastic plasma cell disorder characterized by the proliferation of a plasma cell clone in the bone marrow which produces a monoclonal component that is usually detectable in serum and/or urine.[1] The treatment goals for both young and elderly patients should be to prolong survival by achieving the best possible response, while ensuring quality of life.[2] For young patients, induction followed by high-dose therapy with an autologous stem cell transplant (HDT-ASCT) is the standard of care, and the efficacy of this strategy has been enhanced by the introduction of new drugs as part of the induction therapy. A meta-analysis of four randomized trials showed that bortezomib-based regimens are associated with prolongation of both progression-free survival (hazard ratio, HR=0.75) and overall survival (HR=0.81) with respect to the standard chemotherapy induction regimen.[3] In addition, the use of bortezomib did not compromise peripheral blood stem cell collection.[4] Based on these data, triple-agent induction regimens including bortezomib and dexamethasone, plus a third drug that can be an immunomodulator (thalidomide or lenalidomide), alkylator (cyclophosphamide) or anthracycline, are the new standard induction treatments.[5]

For elderly patients, treatment options were limited in the past to alkylators, but new upfront combinations based on novel agents (proteasome inhibitors and immunomodulatory drugs) plus alkylating agents have significantly improved outcomes. Melphalan and prednisone plus thalidomide or bortezomib is a standard of care for this population of patients. Melphalan and prednisone plus bortezomib is widely used for newly diagnosed elderly MM patients and, following the publication of the results of the VISTA trial,[6] the use of bortezomib has been optimized with weekly, subcutaneous administration that significantly improve tolerability with no effect on efficacy.[7] Lenalidomide plus low-dose dexamethasone, a non-alkylator-based regimen, has been compared with melphalan and prednisone plus thalidomide, with the former regimen resulting superior with regards to both efficacy and outcomes; accordingly, lenalidomide plus low-dose

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dexamethasone is not only another standard of care, but also a new backbone to which novel drugs can be added.[8]

Bendamustine is a unique bifunctional alkylating agent with proven activity in MM.[9] Although it appears to be effective as monotherapy, it is usually combined with other agents, proteasome inhibitors or immunomodulatory drugs. It has an acceptable toxicity profile, and its suitability for patients with renal impairment is of particular note.[10] Although it is commonly used in the relapse setting, bendamustine in combination with prednisone[11] has been approved in Europe in the upfront setting to treat MM patients who are not candidates for HDT-ASCT and who cannot receive thalidomide or bortezomib because they have peripheral neuropathy. The approval was based on a randomized trial in which bendamustine plus prednisone proved to be better than melphalan plus prednisone in terms of complete response rate and time-to-treatment failure.[12]

The combination of bendamustine plus bortezomib and dexamethasone has been tested in seven phase 1-2 trials conducted in relapsed or relapsed and refractory patients, in whom it yielded overall response rates of 48%-85%, with an acceptable safety profile.[9,13] In newly diagnosed MM patients, two studies conducted in transplant-ineligible patients have tested this combination administering bortezomib in the conventional, twice-weekly schedule. The first of these studies included 44 patients, and preliminary results indicated an overall response rate of 85%.[14] The second was a retrospective study conducted in patients with normal or impaired renal function. The overall response rate was 82% and there were no differences between patients with normal/mildly impaired renal function and those with moderate/severe renal impairment.[15]

In this article, we report the efficacy and safety results of the combination of bendamustine plus bortezomib and prednisone (BVP) in newly diagnosed MM patients, but giving bortezomib twice a week during the first cycle and weekly thereafter. This is the first trial conducted in newly diagnosed MM patients which included transplant-eligible and transplant-ineligible patients, and provided a singular opportunity to evaluate the effect of bendamustine on stem cell collection and its efficacy as part of an induction regimen followed by transplantation.

Methods

Patients and study design

Patients with newly diagnosed, untreated, symptomatic, measurable MM were included in this open-label, phase 2 study carried out at 16 centers throughout Spain. All patients received the combination based on BVP: the first cycle consisted of bendamustine 90 mg/m^2 given intravenously (IV) on days 1 and 4, in combination with bortezomib 1.3 mg/m^2 given IV on days 1, 4, 8, 11, 22, 25, 29 and 32 and prednisone 60 mg/m^2 given orally on days 1 to 4. In the following cycles, bendamustine was given on days 1 and 8, and bortezomib on days 1, 8, 15 and 22 (weekly schedule), with prednisone given as previously described (Figure 1). Patients over 65 years old received up to nine 28-day cycles. No maintenance therapy was given. Patients who were candidates for HDT proceeded to peripheral blood stem cell (PBSC) collection after four cycles. PBSC were mobilized with granulocyte colony-stimulating factor (G-CSF) at a dose of 5 μg/kg subcutaneously every 12 h for 5 days. HDT was administered after six cycles using IV melphalan 200 mg/m^2 as the conditioning regimen on days -2 and -1, followed by PBSC infusion.

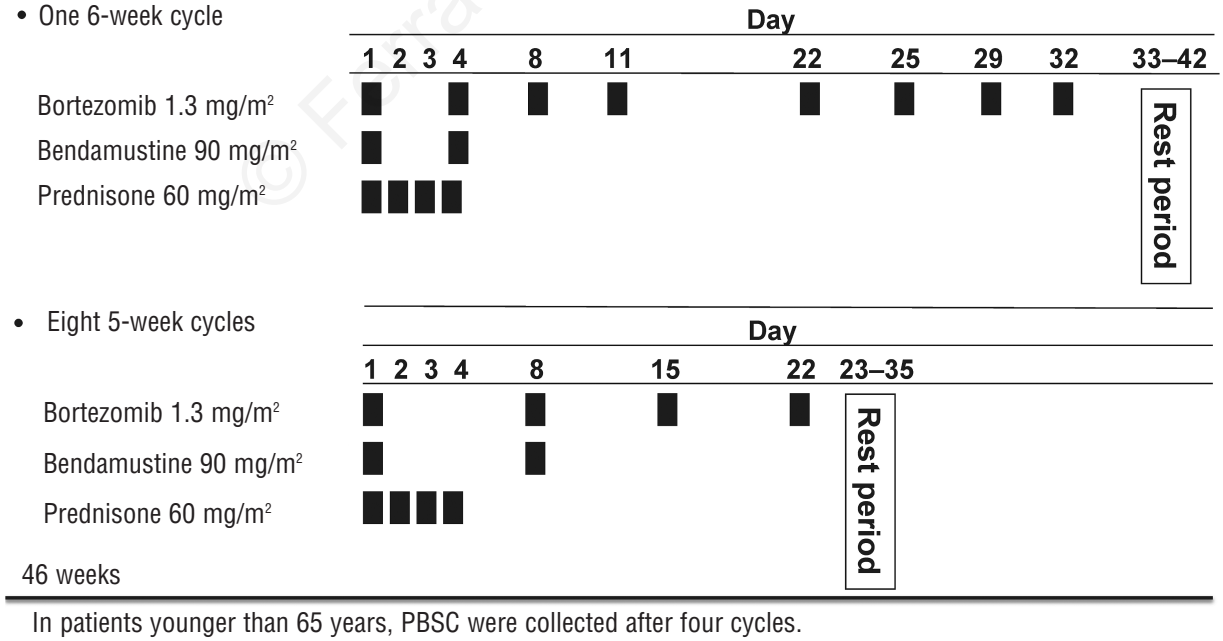

Figure 1. Trial profile.

The Institutional Review Board or Independent Ethics Committee of each participating center approved the study. All patients provided written informed consent before screening. Data were monitored by an external contract research organization and assessed centrally.

Study assessments

Disease response was assessed according to the criteria of the International Myeloma Working Group.[16] Disease response was assessed at the beginning of each induction cycle and at the end of induction. In patients who received HDT-ASCT, disease response was evaluated before and 3 months after ASCT. After the end-of-treatment visit, all patients were followed every 3 months to record their response and outcome. Analysis of minimal residual disease was planned at the end of the induction treatment. Minimal residual disease was analyzed by four-color multiparametric flow cytometry, as previously described.[17] t(4; 14), t(14;16), and 17p deletion were analyzed by fluorescence *in situ* hybridization according to standard procedures using purified plasma cells.[18]

Safety was assessed during the study by monitoring and recording all adverse clinical and laboratory events, which were graded according to National Cancer Institute Common Toxicity Criteria version 4.0.

The primary endpoint was to evaluate the efficacy in terms of response rates, including the different response categories described by the International Myeloma Working Group. Secondary endpoints were to determine safety and tolerability of BVP, as well as efficacy in terms of progression-free and overall survival. In addition, the study was designed to explore the effect of the presence of high-risk cytogenetic abnormalities.

Statistical analyses

Descriptive statistics are provided for demographic and baseline variables.

The intention-to-treat population consisted of all patients included and registered in the trial. The efficacy population consisted of all patients who received at least one cycle of treatment. Survival was analyzed by the Kaplan-Meier method and the log-rank test was used to assess the statistical significance of the comparisons. All statistical analyses were performed using version 15 of the Statistical Package for Social Sciences (SPSS; Chicago, IL, USA).

Table 1. Baseline characteristics.

Characteristics	n=59
Age ≥ 65 years, n. (%) Median, years (range)	19 (32%) 62 (38-82)
Type of M-spike, n. (%) IgG, IgA, BJ	34 (57%) / 13 (22%) / 12 (20%)
ISS stage, n. (%) I/II/III	16 (27%) / 25 (42%) / 18 (30%)
Plasma cell bone marrow infiltration, mean %	27
Serum M-spike, mean, g/dL	3.7
High-risk cytogenetic abnormalities*, n. (%) t(4;14) / t(14;16) / del17p	10 (22%)

*y: years; M-spike: monoclonal spike; BJ: Bence Jones; ISS: International Staging System; *Cytogenetic information from fluorescence* in situ *hybridization was available from 46 patients.*

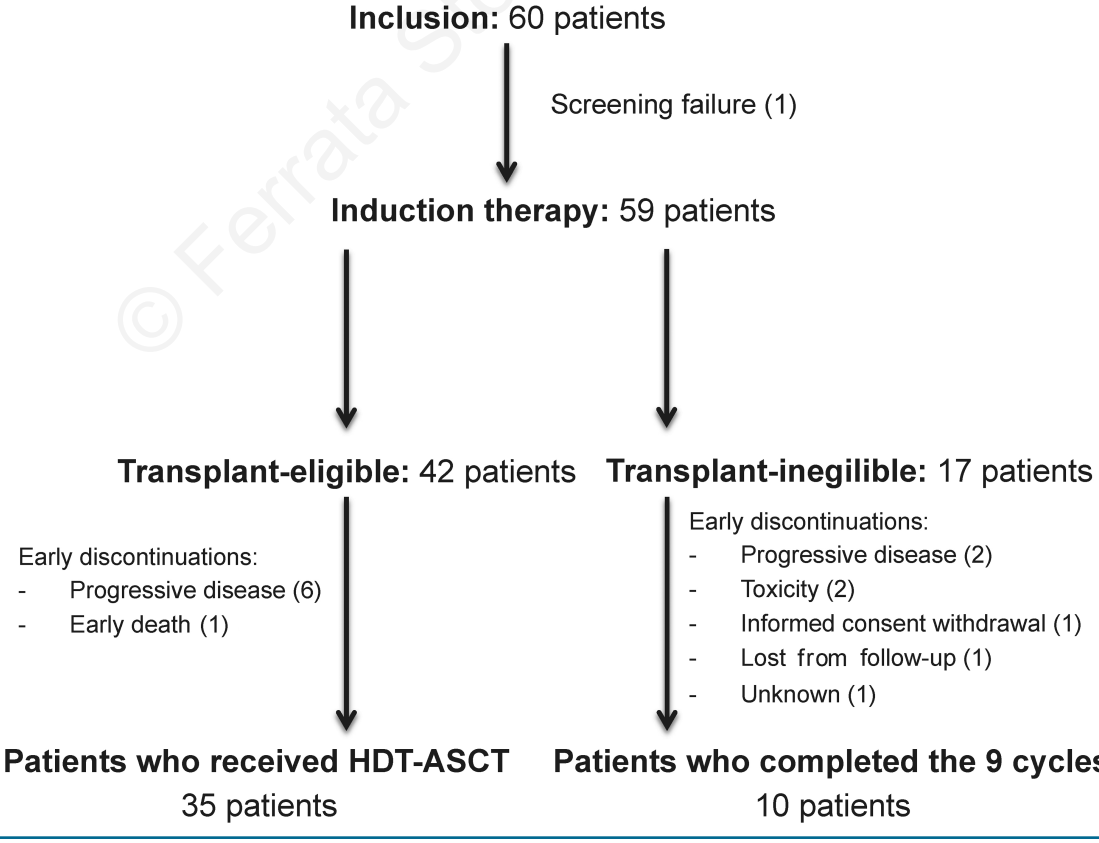

Figure 2. Flow chart of the patients included in the trial.

Results

Patients and distribution

Sixty patients were enrolled between May 2011 and July 2012. The data cut-off for this analysis was July 2014. Baseline characteristics of the patients are summarized in Table 1. Approximately one third of the patients were older than 65 years and 40 of the 60 (67%) were younger than 65 years.

Figure 2 shows the flow chart of the patients included and their distribution during the treatment. Forty-two patients were transplant candidates, but in the end, 35 patients (86%) proceeded to ASCT. Six patients progressed early and one died before the procedure. The group of patients who proceeded to ASCT continued to be followed for progression-free and overall survival. Seventeen patients were not candidates for ASCT and seven of them discontinued treatment early before completing the planned nine cycles because of disease progression (n=2), toxicity (n=2), withdrawal of informed consent (n=2) or an unknown reason (n=1).

Efficacy

In the overall population (n=60), screening was a failure in one patient and another did not complete the first cycle of treatment so efficacy could not be evaluated in these two cases. In the efficacy population (n=58), after a median of six cycles (range, 2-9), 84% of patients achieved at least a partial response, 57% at least a very good partial response (VGPR) and 24% at least a complete response (CR) [10% reaching stringent CR (sCR)]. In general, responses were rapid, the median time to achievement of a partial response being one cycle (range, 1-7) and prolongation of treatment improved the quality of the response: the median time to achievement of a CR was three cycles (range, 2-6).

In the subset of patients who were candidates for HDT-ASCT (n=42), on intent-to-treat basis and after a median of six cycles (range, 2-6), 50% achieved at least a VGPR, including CR in 14% and sCR in 10% of cases. Thirty-five patients received melphalan 200 mg/m^2 and ASCT, and the percentage of patients obtaining VGPR or better rose to 71%, in particular because more patients achieved CR (20%) and sCR (34%).

In the group of patients who were not eligible for transplantation, after a median number of eight cycles (range: 2-9), 57% achieved at least a VGPR, including 13% with CR and 13% with sCR (Table 2).

The presence of high-risk cytogenetic abnormalities, t(4;14), t(14;16) and/or del17p (n=10, 22% of cases), did not influence the response rate and all patients with these abnormalities achieved at least a partial response (80% and 40% achieved a VGPR and CR/sCR, respectively). In the standard-risk group, 84% achieved a partial response or better, including a VGPR in 31% and CR/sCR in 22% of them.

Safety profile

Table 3 summarizes the incidence of adverse events during treatment with BVP in the intention-to-treat group. The most common toxicities of any grade were peripheral neuropathy (38%), neutropenia (32%), asthenia (27%) and infection (27%). However, most adverse events were grade 1-2 (Table 3). No significant differences were observed between patients who were or were not candidates for HDT-ASCT.

Eleven of the previously reported adverse events were considered as serious and included infection in seven patients, and peripheral neuropathy, asthenia, neutropenia and thrombocytopenia in one patient each. Only two patients discontinued treatment early due to toxicity (febrile neutropenia and septic shock). Two patients died early from severe infections (septic shock in 1 patient and pneumonia on day +10 after transplant in the other).

Stem cell collection

Forty patients proceeded to stem cell mobilization after four cycles of BVP. Using G-CSF alone yielded a mean of 3.4x10^6 CD34$^+$ cells/kg (range, 2-7x10^6). However, in 14 patients (35%) a minimum of 2x10^6 CD34$^+$ cells/kg could not be collected after G-CSF alone. An amendment was made and PBSC collection was planned after the third instead of fourth cycle, and plerixafor was recommended for those patients considered to be poor mobilizers because the CD34$^+$ cell count in their peripheral blood was less than 10/μL on day 5 of the mobilization process; with G-CSF plus plerixafor all but two patients achieved the minimum number of CD34$^+$ cells required to proceed to ASCT. In the two patients who did not have the minimum number of CD34$^+$ cells after plerixafor, cells were successfully harvested after administering chemotherapy plus G-CSF and plerixafor.

Survival

The median follow-up for surviving patients was 25 months (range, 5-35). Progressive disease or death

Table 2. Efficacy in terms of response rates to treatment with BVP.

Response status	Overall, n. (%) (n=58)	Trx-candidates, n. (%) (n=42)		Non-trx candidates, n. (%) (n=16)
		Pre-trx (n=42)	Post-trx (n=35)	
Overall response rate (≥PR)	49 (84)	32 (76)	34* (97)	13 (81)
- Stringent complete response	6 (10)	4 (10)	12 (34)	2 (13)
- Complete response	8 (14)	6 (14)	7 (20)	2 (13)
- Very good partial response	19 (33)	11 (26)	6 (17)	5 (31)
- Partial response	16 (28)	11 (26)	8 (23)	4 (25)
- Stable disease	6 (10)	4 (10)	1 (3)	1 (6)
- Progressive disease	3 (5)	6 (14)		2 (13)

*BVP: bendamustine, bortezomib (Velcade) and prednisone; PR: partial response; Trx: transplant. *One patient was not evaluable for response after transplantation because of early death after the transplant.*

Table 3. Toxicity profile of BVP in the intention-to-treat group of patients.

	Grade 1-2, n. (%)	Grade 3-4, n. (%)
Hematologic toxicity		
- Anemia	7 (12)	8 (13)
- Neutropenia	5 (8)	14 (23)
- Thrombocytopenia	5 (8)	9 (15)
Non-hematologic toxicity		
- Asthenia	15 (25)	1 (2)
- Diarrhea	10 (17)	1 (2)
- Constipation	11 (18)	-
- Infections	12 (20)	4 (7)
- Peripheral neuropathy	21 (35)	2 (3)

occurred in 22 patients (38%) in the overall series. The median progression-free survival was not reached and 62% of the patients remained alive and free of progression after 2 years (Figure 3A). Deaths occurred in eight patients (14%) treated with BVP. The median overall survival was not reached and 86% of patients were alive after 2 years (Figure 3B).

The median progression-free survival of transplant candidates, analyzed on an intent-to-treat basis, was not reached and 68% of the patients remained alive and free of progression at 2 years. The 2-year overall survival rate was 87% in this group of patients (Figure 3C). Selecting the 35 out of the 42 patients who finally received HDT-ASCT, the 2-year progression-free survival increased up to 79% and the 2-year overall survival was 97%.

In the patients not eligible for transplantation, the median progression-free survival was not reached and at 2 years, 59% of the patients remained alive and free of progression, with the 2-year overall survival rate being 88% (Figure 3D).

The presence of high-risk cytogenetic abnormalities did not influence the 2-year progression-free survival (80% *versus* 60% in patients with standard risk) (P=0.4). The 2-year overall survival rate of 90% was identical in patients with high-risk and standard-risk cytogenetic abnormalities.

Achievement of CR/sCR influenced the time to progression (TTP), and after 2 years, only two patients who achieved CR had relapsed, resulting in a 2-year TTP rate of 85% compared with 59% in the group of patients who did not achieve CR (P=0.1).

The prognostic value of minimal residual disease monitoring by multicolor flow cytometry was assessed in the cohort of 35 patients in whom this sub-analysis was performed. Thirteen patients (37%) achieved immunophenotypic CR, which translated into longer TTP (2-year TTP rate 77% *versus* 43%; P=0.08) and overall survival (2-year overall survival 100% *versus* 76%; P=0.05).

Discussion

This study shows that bendamustine in combination with bortezomib and prednisone, in a regimen using only an intensive dose of bortezomib twice weekly in the first cycle, followed by a weekly dose, is effective and safe in newly diagnosed transplant-eligible and transplant-ineligible MM patients. Results from trials evaluating BVP in newly diagnosed MM patients have only been published in abstract form[14] or have been derived from retrospective analysis.[15] In addition, this trial evaluates for the first time the effect of BVP on stem cell collection and its efficacy as an induction regimen followed by transplantation.

As mentioned above, only two studies have evaluated the BVP regimen in newly diagnosed MM patients. Pönisch *et al.* reported that 53% of a series of 49 newly diagnosed MM patients achieved a VGPR or better, showing that the combination was equally effective in patients with normal or impaired renal function.[15] However, the retrospective nature of this study as well as the differences in the baseline characteristics of the patients precludes comparisons with our trial. Berdeja *et al.*[14] conducted a

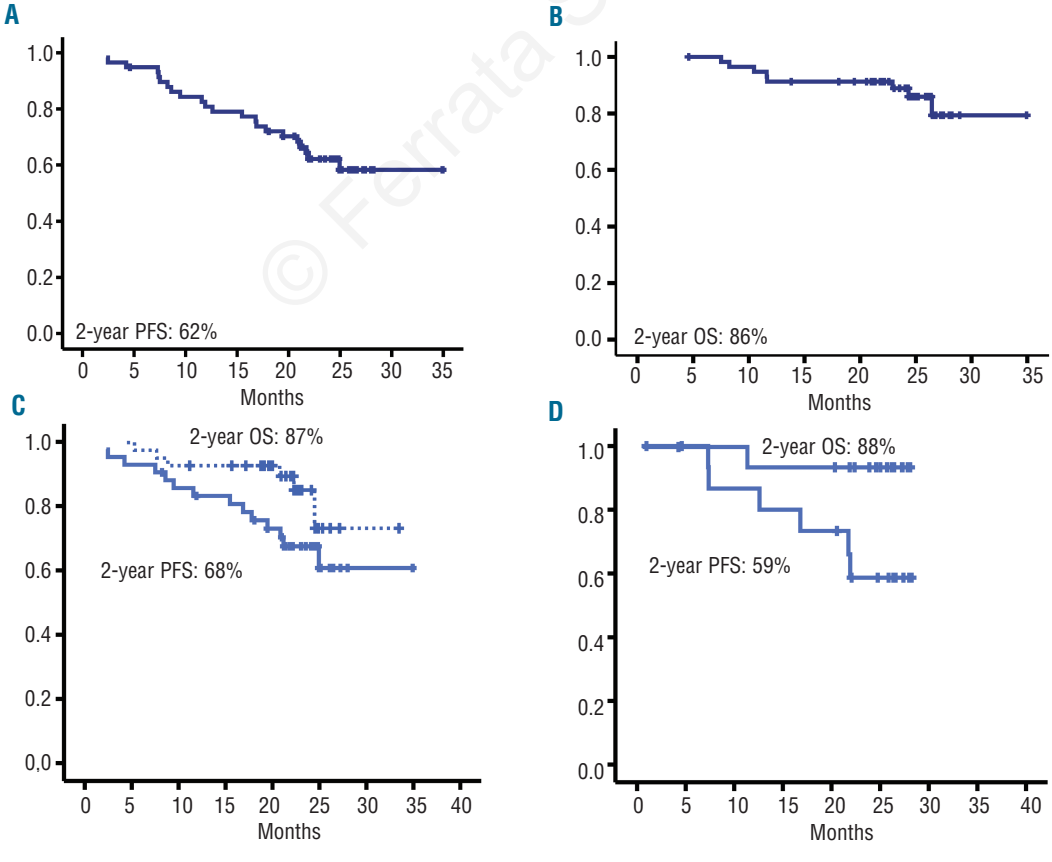

Figure 3. (A) Progression-free survival (PFS) and (B) overall survival (OS) in the whole series. Progression–free survival and overall survival in (C) transplant-eligible patients and (D) transplant-ineligible patients.

prospective trial evaluating BVP in 44 newly diagnosed MM patients, all of whom were ineligible for transplantation. The preliminary results, reported at the American Society of Hematology meeting in 2013, indicated that 59% of the patients achieved a VGPR or better, including 11% with CR, and the median progression-free survival was 14 months. The efficacy observed in our trial seems to be greater, with 24% obtaining sCR/CR, although it included transplant and non-transplant candidates. Considering only the 17 transplant-ineligible patients, the sCR/CR rate (26% *versus* 11%) and the progression-free survival rate (59% at 2 years *versus* 14 months) were slightly higher than in the trial by Berdeja *et al.* A limitation of our trial is the small number of transplant-ineligible patients included, and although this makes it difficult to compare our results with the standards of care in non-transplant candidate patients, the optimal comparison would be between this regimen and the trial of bortezomib, melphalan and prednisone (VMP) developed by a Spanish group, in which 130 patients received nine VMP cycles with an identical bortezomib schedule but melphalan instead of bendamustine[19] The rates of partial response or better produced by BVP and VMP were 81% and 78% (including 26% and 21% with sCR/CR), respectively. The Italian Myeloma Group also evaluated nine cycles of VMP, in which bortezomib was given weekly to non-transplant eligible patients, and found a CR rate of 24% which is similar to that in our trial.[20]

In transplant candidates, six cycles of BVP as induction therapy yielded a rate of VGPR or better of 50%, including 24% with sCR/CR; these efficacy results are slightly lower than those obtained after six cycles of bortezomib plus thalidomide and dexamethasone (VGPR or better in 60% and CR in 35% of cases).[21] During the induction, patients received prednisone instead of dexamethasone, which is more commonly used in the induction regimens for transplant candidates and is a more effective debulking drug. Melphalan 200 mg/m^2 followed by ASCT raised the responses rates to 34% sCR and 20% CR, which are also similar to the 57% CR rate observed after induction with six cycles of bortezomib, thalidomide and dexamethasone followed by transplantation.[21]

However, PBSC mobilization after four cycles of BVP was a major concern in our trial, since 35% of the patients did not produce enough CD34$^+$ cells/kg to proceed to ASCT. Pönisch *et al.* retrospectively analyzed 56 MM patients who had undergone stem cell mobilization after bendamustine treatment, but cyclophosphamide alone or a cyclophosphamide-containing regimen was used for mobilization in all patients.[22] In our trial, G-CSF alone was chosen for mobilization and the protocol required urgent amendment to perform the mobilization after the third cycle; plerixafor was prescribed for those patients who had fewer than 10^6 CD34$^+$ cells/L in peripheral blood on day 5 of mobilization with G-CSF alone. This pre-emptive strategy was able to reduce the number of remobilization sessions, thereby saving financial resources and avoiding delays in the transplant program.[23,24] All mobilization failures were rescued with plerixafor, except in two patients who required chemotherapy.

The toxicity profile was acceptable. The most frequent grade 3-4 hematologic adverse event was neutropenia, which occurred in 23% of the patients. Although this event did not result in a high frequency of severe infections (7%), secondary prophylactic G-CSF use should be considered in the case of severe neutropenia. Only two patients developed grade 3 peripheral neuropathy, but further treatment optimization would include the use of bortezomib administered subcutaneously, which was not available when the trial was developed.

Although the number of patients included in this trial is rather small to draw conclusions, our results confirm the previously reported role of CR/sCR as well as of immunophenotypic response as a relevant prognostic factor in MM for both transplant-eligible and transplant-ineligible patients.[25,26]

In summary, the results of this phase 2 trial of BVP in untreated MM patients are encouraging, although the conclusions should be interpreted with caution due to the sample size and the single-arm, non-randomized design. The regimen had an acceptable toxicity profile. In transplant-ineligible candidates, bendamustine seems not to be superior to melphalan in combination with bortezomib, while in transplant candidates, bendamustine as part of the induction, followed by HDT-ASCT, shows comparable efficacy to bortezomib, thalidomide and dexamethasone, although it appears to compromise PBSC mobilization with growth factors alone, and cyclophosphamide or plerixafor should always be considered.

The rapid introduction of second- and third-generation proteasome inhibitors and immunomodulatory drugs, as well as monoclonal antibodies with marked activity in the upfront setting, will represent a challenge to the BVP scheme. Accordingly the current combination will probably be better reserved for relapsing patients, in whom stem cell collection is not needed and cost-effective combinations with non-cross-resistant drugs continue to be needed.

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Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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