Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study

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Background and objectives. Induction regimens prior to autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma patients usually result in complete remission (CR) rates of <10%. The use of novel agents may increase the CR rate before ASCT, which may improve post-transplantation response and survival.

Design and methods. This was a phase II, open-label trial of bortezomib (1.3 mg/m^2, days 1, 4, 8, 11) and dexamethasone (40 mg, days 1–4 and 9–12 for cycles 1–2, days 1–4 for cycles 3–4) administered for four 21-day cycles as induction therapy in chemotherapy-naïve myeloma patients.

Results. Of 52 recruited patients, 48 were eligible for the study. The overall response rate was 66% including 21% CR and 10% very good partial remission (>90% reduction of the M-component). Four patients had a minimal response, six had stable disease and five had progression. One patient died after salvage therapy with VAD. The most common side effects were gastrointestinal symptoms, peripheral neuropathy, and fatigue. These were usually mild. Peripheral neuropathy was observed in 15 cases but was grade 2-3 in only seven cases (14%). There was no deep vein thrombosis and no hematologic toxicity greater than grade 2. Grade 3 infections were recorded in five patients including three who had herpes zoster infections. Stem cell collection was programmed in 44 cases and all patients had sufficient CD34$^+$ cells to perform one ASCT (> 2×10^6/kg).

Interpretation and conclusion. This regimen of bortezomib plus dexamethasone appears effective and well tolerated in newly diagnosed myeloma patients.

Key words: bortezomib, clinical trial, dexamethasone, multiple myeloma, stem cell transplantation.

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Autologous stem cell transplantation (ASCT) is considered the standard of care for patients up to 65 years of age with multiple myeloma (MM).[1-4] While in randomized studies the median survival of younger patients with MM treated with conventional chemotherapy is 40-42 months, the use of high-dose therapy with ASCT increases median survival to 54-57 months.[2] Although the impact of complete remission (CR) achievement on survival is still a matter of debate,[5,6] in most high-dose therapy protocols, survival appears to be significantly related to the magnitude of response.[2,3,5,7-9] In the Intergroupe Francophone du Myélome (IFM) IFM90 and IFM94 trials, survival was longer for patients who achieved CR or very good partial remission (VGPR) than for patients who had a partial response (PR). This was confirmed in the IFM99 trials (*H. Avet-Loiseau, personal communication*). The usual preparative regimen given prior to ASCT is melphalan 200 mg/m^2.[10] Until now, there has been no convincing evidence that any preparative regimen is superior to melphalan 200 mg/m^2.[10,11] Therefore, one way to improve the rate of CR + VGPR after ASCT may be to improve the efficacy of the induction treatment. One of the combination regimens most commonly used prior to ASCT is vincristine, doxorubicin, and dexamethasone (VAD); another is vincristine, doxorubicin, and methylprednisone (VAMP). However, with these induction treatments, the CR rate, which depends on the response criteria utilized as well as the number of treatment cycles received, is usually <10%.[4,10,12-15] The introduction of novel agents such as thalidomide or bortezomib provides an opportunity to improve induction therapy prior to ASCT. Bortezomib (VELCADE®, formerly PS-341, Millennium Pharmaceuticals, Inc., and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.) is a completely novel approach to treating MM because it acts on a unique target in cells, the proteasome. Bortezomib is a potent, selective, and reversible proteasome inhibitor that inhibits the degradation of ubiquitinated target proteins, such as p53, p21 and p27, which are critical for cell cycle regulation and apoptosis

in normal and malignant cells.[16] These effects are partly mediated through inhibition of the nuclear factor-κB pathway, which has been shown to be important in multiple myeloma.[17] Bortezomib yielded high response rates in heavily pretreated patients in the phase II SUMMIT and CREST trials.[18,19] The APEX randomized phase III trial has shown that bortezomib is superior to high-dose dexamethasone in the treatment of patients with relapsed MM, following one to three prior therapies.[20] Patients receiving bortezomib had significantly improved time to progression and survival and higher response rates. Bortezomib has a predictable safety profile and a favorable benefit-to-risk ratio. It is now approved in the United States for the treatment of MM patients who have received at least one prior therapy. The European Agency for the Evaluation of Medicinal Products (EMEA) has approved bortezomib as second-line treatment in patients with MM who have already undergone or are unsuitable for stem cell transplantation. This novel agent is currently being evaluated in a number of clinical trials as part of front-line therapy in patients with MM.

In vitro studies have indicated that the combination of bortezomib and dexamethasone may be additive or possibly synergistic.[21] In SUMMIT and CREST, the addition of dexamethasone (160 mg in 3 weeks) in patients with a less than optimal response to bortezomib alone yielded improved outcomes.[18,19] In the front-line setting, the addition of dexamethasone (at an intensity slightly less than that used in high-dose pulse therapy, namely 320 mg in a 3-week cycle) in patients with a less than optimal response to bortezomib monotherapy prior to stem cell transplantation improved the outcome in 23 of 36 patients (64%), with a 90% overall response rate and a 19% CR plus near CR rate.[22,23] The primary objective of this phase II, multicenter, open-label trial was to determine the CR rate achieved after four cycles of bortezomib plus dexamethasone combination therapy in patients with newly diagnosed MM who were candidates for ASCT. However, the addition of dexamethasone to bortezomib could increase toxicity, especially since in this study, unlike in SUMMIT,[18] CREST,[19] and the front-line study by Jagannath,[22,23] dexamethasone was administered to all patients from the very start. Therefore, the secondary objectives were to determine the overall response rate and the safety profile of this combination including its impact on autologous stem cell collection.

Design and methods

Patients' selection

Eligibility criteria for this study included a diagnosis of MM according to the Southwest Oncology Group (SWOG) criteria age ≤75 years, absence of active systemic infection, and no childbearing potential or use of adequate contraceptive measures. Patients had to be previously untreated, with the exception of prior localized radiation therapy, have symptomatic stage II or III disease according to the Durie-Salmon staging system or stage I disease with one symptomatic osteolytic lesion, and have measurable levels of monoclonal (M)-protein in the serum (≥1g/dL) or in the urine (≥0.2 g per 24 hours). Patients were excluded from the study if they met one or more of the following conditions: life expectancy <2 months; Eastern Cooperative Oncology Group (ECOG) performance status >2; proven amyloidosis; serological evidence of human immunodeficiency virus infection; psychiatric disease; severe diabetes contraindicating the use of high-dose corticosteroids; National Cancer Institute (NCI) grade ≥2 peripheral neuropathy; creatinine level > 200 μmol/L; bilirubin, transaminases, or γ-glutamyltransferase >3 times the upper limit of normal; and the following hematologic values: platelets $<30\times10^9$/L or absolute neutrophil count $<1.0\times10^9$/L within 14 days of enrollment. Patients were also excluded if they had received any experimental drugs within 30 days of enrollment. There were no protocol recommendations regarding prophylactic antibiotics or any other supportive care. Each institution followed its own guidelines. All patients provided informed consent, and the trial was approved by the Regional Ethics Committee of Pays de la Loire and by the Institutional Review Board of each participating center, and was performed in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Study design

This open-label, multicenter, non-comparative, phase II study investigated the efficacy and safety of bortezomib 1.3 mg/m^2 in combination with high-dose dexamethasone as initial therapy in patients with newly diagnosed MM. The primary objective of the study was to determine the CR rate achieved after four cycles of bortezomib plus dexamethasone in patients with newly diagnosed MM who were candidates for ASCT. The secondary objectives were to determine the response rate, including CR, PR, and minimal response (MR), to determine the rates of stable disease (SD) and progressive disease (PD), to determine the safety profile of the combination of bortezomib and dexamethasone, and to determine the impact of bortezomib plus dexamethasone on ASCT (target yield, 5×10^6 CD34$^+$ cells/kg).

Drug administration

The combination of bortezomib and dexamethasone was administered for four consecutive 21-day cycles. Bortezomib was administered intravenously (IV) at a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 of each cycle. Dexamethasone 40 mg was administered orally on days 1–4 and 9–12 for the first two cycles and on days 1–4 only for the following two cycles. Bacterial infection

prophylaxis with Bactrim® was recommended, while herpes/herpes zoster prophylaxis was not. Before each bortezomib dose, the patient was evaluated for possible toxicity according to the NCI Common Toxicity Criteria, version 2.0. If grade 4 hematologic toxicity, febrile neutropenia, or any grade ≥3 non-hematologic toxicity related to bortezomib occurred, bortezomib was withheld until toxicity returned to grade ≥1 (excluding peripheral neuropathy). If the toxicity did not resolve within 2 weeks, bortezomib was discontinued. If the toxicity resolved, bortezomib was restarted at a dose reduced by 25%. Peripheral sensory neuropathy or neuropathic pain was managed according to specific guidelines.[24] Bortezomib was to be discontinued in the event of grade 4 peripheral neuropathy.

Response criteria

Blood and urine samples were collected at baseline, before each of the following 21-day cycles, and 4 weeks after the fourth cycle. Response to therapy was assessed before cycle 3 and cycle 4, and 4 weeks after cycle 4. Achievement of CR required confirmation 28 days later. In order to be able to make comparisons with our previous experience, we applied the response criteria used in prior IFM trials.[2,7] CR was defined by the disappearance of M-protein assessed by serum and/or urine electrophoresis and ≤5% plasma cells in the marrow, VGPR was defined as ≥90% reduction of the serum M-protein, and PR as ≥50% reduction of the serum M-protein or ≥90% reduction of the urinary M-protein. As in previous IFM studies, immunofixation was not mandatory for the assessment of CR.

MR was defined as ≥25% reduction in serum M-protein or ≥50% reduction in urinary M-protein. The designation of SD was reserved for patients who failed to meet the criteria for CR, PR, MR, or PD. PD was defined as > 25% increase in M-protein on two separate measurements at 4-week intervals. Because all eligible patients received more than one complete cycle, all were analyzed for both safety and efficacy. In addition, two ineligible patients received the study drugs and were analyzed for safety only.

Stem cell harvest procedure and stem cell transplantation

Stem cell collection was to be performed after cycle 3. Stem cells ($CD34^+$) were collected after priming with granulocyte colony-stimulating factor (G-CSF) alone (10 μg/kg per day from days 17–23). One to three harvests were performed starting on day 21. The $CD34^+$ cell count in the blood (minimum target, 20/μL) was evaluated before each stem cell collection. The target yield was 5×10^6 $CD34^+$ cells/kg, which is the dose considered necessary to ensure safe engraftment in a double ASCT procedure. If stem cell collection was not adequate after cycle 3, a second collection was made after cycle 4, following priming with a combination of cyclophosphamide 3 g/m^2 IV plus G-CSF 5 μg/kg per day. The patients were prepared for the stem cell transplantation with melphalan 200 mg/m^2.

Fluorescence in situ hybridization (FISH) analysis

After purification of bone marrow plasma cells using anti-CD138–coated magnetic beads,[25] interphase analysis was performed with probes specific for the following chromosomal changes: chromosome 13 deletions, translocations t(4;14) and t(11;14), and deletion of 17p.

Statistical considerations

In this phase II pilot study, designed to rapidly evaluate the efficacy and safety of the combination of bortezomib and dexamethasone, formal statistical hypothesis testing was not performed. After treatment of the first 20 patients, an interim analysis was performed, mostly to assess safety parameters. Because the toxic death rate with VAD is up to 5%, the study was to be stopped if four or more toxic deaths occurred after treatment of 20 patients. As there was only one death and 70% responses at the time of this analysis, the study was continued.

Results

Demographics

Fifty-two patients were recruited between April and August 2004; four patients were ruled ineligible (one with renal failure and three with unmeasurable M-protein). The demographic and baseline characteristics for all patients who received the study drugs (n=50) are shown in Table 1. Slightly more men than women were enrolled, and the median age was 55 years. The Durie Salmon stage was I, II, and III in 4, 14, and 32 patients, respectively. When stratified according to the International Staging System[23] there were 20, 20, and 10 patients in stages I, II, and III, respectively. FISH analysis was performed: del(13) was present in 41% (18/44) of cases, t(11;14) in 26% (9/35) of cases, t(4;14) in 11% (4/35) of cases, and del(17p) in 11% (4/33) of cases; one patient had both t(4;14) and del(17p).

Drug exposure and patient disposition

Feasibility data are presented in Table 2. Of 50 patients who received at least one cycle of treatment (including two patients who were ruled ineligible due to unmeasurable disease), 41 (82%) received four cycles for a total of 16 doses of bortezomib (full treatment), one patient (2%) received 14 doses (doses withheld because of peripheral neuropathy), seven patients (14%) received 12 doses (dose withheld in one patient because of peripheral neuropathy, in another because of acute respiratory distress syndrome possibly related to infection, and in five because of SD or PD), and one patient

Table 1. Characteristics of the patients (n=50).

Characteristic	
Sex: M/F, n	28/22
Median age, y (range)	55 (38–71)
Durie-Salmon stage I/II/III, n	4/14/32
Durie-Salmon stage A/B, n	47/3
Isotype: IgG/IgA/LC/others, n	24/13/10/3
Light chain: κ/λ, n	35/15
Median creatinine, µmol/L (range)	89 (25–187)
Median calcium, mmol/L (range	2.37 (1.61–3.01)
Median β_2-microglobulin, mg/L (range)	3.1 (1.2–11.5)
Median hemoglobin, g/dL (range)	10.9 (7.9–15.0)
Median platelet level, 10^9/L (range)	228 (65–319)
Median CRP, mg/L (range)	4 (0–52)
Median albumin, g/L (range)	38 (23.5–49)
Median bone marrow plasma cells, % (range)	34 (2–88)
ISS stage I, n	20
ISS stage II, n	20
ISS stage III, n	10
FISH analysis	
del(13)	18/44 (41%)
t(11;14)	9/35 (26%)
t(4;14)	4/35 (11%)
del(17q)	3/33 (9%)

Ig: immunoglobulin; LC: light chain; CRP: C-reactive protein; ISS: International Staging System; FISH: fluorescence in situ hybridization.

Table 2. Drug exposure (n=50).

Description of treatment characteristics	*No. patients (%)*
Full treatment (4 courses, 16 doses)	41 (82)
Reason that bortezomib was withheld:	
Peripheral neuropathy	1* (2)
	1
Reasons that bortezomib was discontinued:	8† (16)
Peripheral neuropathy	1
ARDS	1
SD or PD	6
Toxicity leading to bortezomib dose reduction:	4
Rash	1
Gastrointestinal	1
Peripheral neuropathy	2
Dexamethasone dose reduction:	2
Infection	2
Total n. of patients with:	
Adverse events	44 (88)
Serious adverse events	7 (14)
Patient withdrawal due to toxicity:	3
Peripheral neuropathy	2
ARDS	1

*ARDS: acute respiratory distress syndrome; SD: stable disease; PD: progressive disease. *Patient received a total of 14 doses of bortezomib. †Seven patients received 12 doses of bortezomib, and one patient received nine doses of bortezomib.*

received nine doses (doses withheld because of PD). Six of the eight patients who received 12 to 14 doses received second-line salvage therapy, and two of eight patients proceeded directly to stem cell collection and ASCT (one patient in CR with peripheral neuropathy and one patient with SD). The dose of bortezomib was reduced in four patients because of toxicity, in the form of rash (n=1), gastroinstestinal toxicity (n=1) or peripheral neuropathy (n=2) and the dose of dexamethasone was reduced in two patients (n=2) secondary to infection (n=2) (*physician's choice*).

Safety

All patients who received the study drugs were evaluable for safety. The incidences of the most commonly reported adverse events are presented in Figure 1. Forty-four patients (88%) had adverse events, and seven (14%) experienced serious adverse events, defined as any event that resulted in death, was life-threatening, required hospitalization, resulted in persistent or significant disability, or had important medical consequences. There was no treatment-related mortality. Three patients withdrew due to toxicity (two because of peripheral neuropathy and one because of acute respiratory distress syndrome possibly related to infection). The vast majority of adverse events were grades 1 and 2 and most commonly involved the gastrointestinal tract. Grade 3 events included infections in five patients (pneumonia in two and herpes zoster infections in three), peripheral neuropathy in three patients, hepatotoxicity in two patients (transient elevation of alkaline

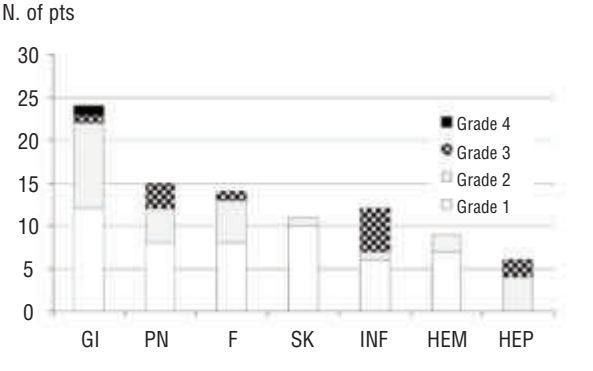

Figure 1. Toxicity: incidence of the most commonly reported adverse events (N=50). Infection (INF) included one case of grade 2 bronchitis, two cases of grade 3 pneumonia and three herpes zoster infections. GI: gastrointestinal toxicity; PN: peripheral neuropathy; F, fatigue; SK: skin toxicity; HEM: hematologic toxicity; HEP: hepatotoxicity.

phosphatases in one patient, of alkaline phosphatases and transaminases in one patient) and gastrointestinal toxicity, fatigue, infection, and rash in one patient each. A single grade 4 event (transient intestinal obstruction) was observed. There was no deep vein thrombosis or pulmonary embolism. Seven patients were hospitalized because of serious adverse events, including three who had severe infection during therapy. Hematologic toxicity was very mild. Only one case of grade 2 thrombocy-

Table 3. Efficacy (intention-to-treat analysis).

Evaluable patients	*Two cycles (n=47)**	*Three cycles (n=45)†*	*End of treatment‡ (n=48)*
Complete response	3	5	10 (21%)
VGPR	1	5	5 (10%)
Patients response	28	20	17 (35%)
Minimal response	8	7	4 (8%)
Stable disease	6	6	6 (13%)
Progressive disease	1	2	5§ (10%)
Death	0	0	1 (2%)

**Data not available for one patient. †Data not available for three patients. ‡Including patients who stopped treatment prematurely. §Three patients who initially responded later progressed on therapy.*

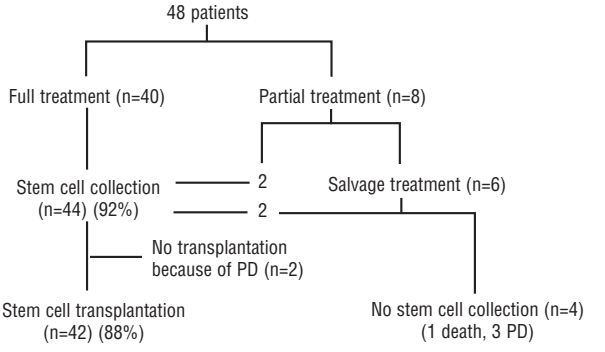

Figure 2. Feasibility of stem cell collection and stem cell transplantation in evaluable patients. PD indicates progressive disease.

topenia was reported. Of the seven patients with baseline platelet counts < 150×10⁹/L, only two had episodes of thrombocytopenia (grade 1). Peripheral neuropathy was observed in 15 cases (30%) but was grade 2-3 in only seven cases (14%). Of the three patients with grade 3 peripheral neuropathy, the neuropathic symptoms improved to grade 1 in each case after drug withdrawal or dose reduction.

Efficacy

The efficacy data (on a modified intention-to-treat basis) are shown in Table 3. Ten patients (21%) achieved CR, five (10%) achieved VGPR and 17 (35%) had a PR. Four additional patients had MR. Six patients had stable disease and five progressed while receiving therapy. The patient who stopped bortezomib due to respiratory distress syndrome subsequently received two courses of VAD but died with neurologic symptoms after the second course. The overall response rate (CR+VGPR+PR) was 66%. Although the best response rate was 73%, only the response rate at the end of treatment was considered since three patients who initially responded later progressed on therapy and were therefore classified as having PD. The CR + VGPR rate was 31%. The CR rate increased from 6% after two cycles to 21% after four cycles. Likewise, the VGPR rate increased from 2% after two cycles to 10% after four.

The CR + VGPR rate did not appear to be related to initial prognostic characteristics (Durie-Salmon or ISS stage, β2-microglobulin level) (*data not shown*). Of 18 patients with del(13), two had CR, four had VGPR (CR+VGPR rate 33%) and six had PR with a total response rate of 67%. The CR + VGPR rate and the overall response rate were identical to those achieved in patients without del(13) (30% and 63%, respectively). The patient with both t(4;14) and del(17p) progressed on therapy while, out of the six patients with either abnormality, four had a PR, one had a VGPR and one achieved CR.

Stem cell harvest and transplantation

After priming with G-CSF alone (10 μg/kg per day from days 17-23), stem cell harvest was performed in 42 of 48 patients following therapy with bortezomib plus dexamethasone (88%) (Figure 2). In 39 cases, the stem cells were collected after the third cycle, and in three cases, after the fourth cycle. The median number of cytapheresis procedures was two (range, 1-4). In two additional patients, stem cells were harvested after a second-line salvage regimen (VAD or dexamethasone, cyclophosphamide, etoposide, and cisplatin [DCEP]). Stem cells were not collected from four patients (one patient died before the collection could be performed; three patients had PD). The median number of $CD34^+$ cells collected was 6.7×10^6/kg (2.0 to 33.8×10^6/kg). All patients had enough CD34+ cells to perform one ASCT (>2 $\times10^6$/kg). However, in 12 patients (27%), the $CD34^+$ cell yield was not sufficient to support double ASCT (less than the defined target yield of 5×10^6/kg). These patients did not differ with regard to initial characteristics, age, or response to treatment from the 32 patients in whom the stem cell yield was ≥5×10^6/kg.

Overall, 42 of 48 evaluable patients (88%) could proceed to ASCT, including 40 patients who received only bortezomib plus dexamethasone. Two patients with an available graft did not undergo ASCT because of disease progression. After ASCT the outcome was as follows: 14 of 42 patients (33%) achieved CR, nine of 42 patients (21%) achieved VGPR, 15 of 42 patients (36%) achieved PR, and four of 42 patients (10%) achieved MR. The CR+VGPR rate for the 42 patients who underwent transplantation was 55%. Overall, on an intention-to-treat basis, the CR+VGPR rate was 48%.

Discussion

In patients who are candidates for ASCT, the treatment usually begins with three or four courses of induction chemotherapy, with the objective of reducing

tumor cell mass prior to high-dose therapy without limiting stem cell mobilization or reducing the quality of the hematopoietic graft. In this context, VAD and VAMP have been the standard induction therapies, because these regimens are not toxic to normal bone marrow progenitors and induce rapid responses.[14,27] Although the response rate to these regimens is acceptable, the CR rate is usually low (<10%) and depends on the number of courses and on how CR is defined. Although some investigators have used bolus injections of vincristine and doxorubicin,[28] VAD is usually administered as a 4-day continuous IV infusion, which requires a central line and increases the risk of catheter-related infections and thrombosis.[27] Finally, there are concerns regarding the value of vincristine and doxorubicin, which have marginal activity in MM[29] and increase toxicity. Many investigators think that dexamethasone contributes to most of the activity of VAD,[27] and in the United States, dexamethasone has been used alone as induction therapy prior to ASCT.[30] The introduction of novel agents such as bortezomib or thalidomide and its analogs provides an opportunity to improve induction therapy prior to ASCT. The aim of this phase II study was to evaluate the efficacy and safety of bortezomib plus dexamethasone as induction therapy in patients with newly diagnosed MM who were candidates for ASCT. Regarding efficacy, the overall response rate in an intention-to-treat analysis (including patients who did not receive the four planned courses) was 66%. The CR rate, which was the primary focus of the study, was 21% using the criteria defined by the IFM, which are based only on serum/urine electrophoresis and bone marrow evaluation. Although the EBMT criteria are now becoming commonly used, the IFM definitions are still based on these simple criteria,[2,7] which have been shown to be of prognostic significance, while the impact of *true* CR defined by immunofixation is controversial.[7,31-33]

In addition, 10% of patients achieved VGPR, defined by a 90% reduction of serum M-component. Both the CR rate (21%) and the CR+VGPR rate (31%) achieved with bortezomib plus dexamethasone compare favorably with results obtained with VAD prior to ASCT in other studies of patients with newly diagnosed disease (Table 4).[4,7,10,12-14,34] In our own experience, the CR+VGPR rates in patients recruited in the IFM 94 and IFM 95 02 trials were only 12% and 13%, respectively, following VAD therapy.[7,10] In a recent study comparing VAD and thalidomide/dexamethasone, the CR + VGPR rate was 14% with VAD and 19% with thalidomide/dexamethasone.[34] Chromosome 13 deletion and/or presence of other cytogenetic abnormalities associated with a poorer outcome did not appear to have an impact on the response rate. However, the number of patients was too small to draw definite conclusions and to confirm preliminary indications that chromosome 13 abnormalities have no effect on response to bortezomib.[35,36] With two blocks of dexamethasone in the first two cycles and only one in the following two cycles, the regimen under investigation in this study was well tolerated. Overall, 82% of patients received the planned 16 injections of bortezomib. As in other trials testing bortezomib alone or in combination, adverse events were mostly mild and grade 1 or 2 in severity. Peripheral neuropathy was observed in 15 patients (30%) but was grade 3 in only three patients (6%). The entire treatment was administered on an outpatient basis, and only seven patients had to be hospitalized for serious adverse events (including three infections). One patient had severe acute respiratory distress syndrome which could have been related to an infection. However a Japanese group recently described severe pulmonary complications after bortezomib treatment for refractory MM.[21] Three herpes zoster infections were recorded (6%), an adverse event already noted in the APEX randomized trial in relapsed patients (n=20).[37] Hematologic toxicity was minimal, with only one case of grade 2 thrombocytopenia; thrombocytopenia >grade 1 was not observed in the seven patients whose initial platelet counts were low. No deep vein thrombosis or pulmonary embolism was recorded, whereas this complication has been observed in approximately 15% newly diagnosed patients treated with a combination of thalidomide and dexamethasone.[34,38] Importantly, there were no toxic deaths while toxic death rates of 3-5% have been associated with higher doses of dexamethasone alone or in combination (VAD or thalidomide/dexamethasone).[34,38]

An important issue was the impact of the combination of bortezomib and dexamethasone on ASCT. Stem

Table 4. Comparison of results achieved with bortezomib plus dexamethasone and with VAD or thalidomide plus dexamethasone prior to autologous stem cell transplantation.

	No. patients	*CR rate%*	*CR+VGPR rate%*
Bortezomib+dexamethasone			
Present study	48	21*	31
VAD			
Palumbo *et al.* 2004[4]	95	5*	NA
Attal *et al.* 2003[7]	399	NA*	12
Moreau *et al.* 2002[10]	399	4†	13
Lenhoff *et al.* 2000[12]	274	4*	NA
Barlogie *et al.* 1999[13]	231	5†	NA
Segeren *et al.* 2003[37]	379	2†	NA
Cavo *et al.* 2005[34]	100	13‡	14
VAMP			
Raje *et al.*1997[14]	75	8*	NA
Thalidomide + dexamethasone			
Cavo *et al.* 2005[34]	100	13‡	19
Rajkumar *et al.* 2004[35]	99	4	NA

*VAD: vincristine, doxorubicin, dexamethasone; CR: complete response; VGPR: very good partial response; VAMP: vincristine, doxorubicin, methylprednisolone. *Defined by electrophoresis. †Defined by immunofixation. ‡CR (negative immunofixation) plus near CR (positive immunofixation).*

cell harvest was performed in 44 of 48 patients, and 42 patients proceeded to ASCT; two patients progressed before ASCT. The median number of $CD34^+$ cells was 6.7×10^6/kg. All harvests contained enough $CD34^+$ cells to support at least one ASCT (2×10^6/kg). Other trials have demonstrated the feasibility of stem cell collection and ASCT after front-line therapy with bortezomib alone or in combination.[22,23,39] However, the target $CD34^+$ cell yield was 5×10^6/kg in order to support double ASCT, since the IFM 94 trial has shown that double ASCT is superior to single ASCT.[7] This target cell yield was obtained in only 73% of patients from whom stem cells were collected after priming with G-CSF alone. In the IFM99-01 trial, after induction chemotherapy with VAD, patients were randomly assigned to receive either cyclophosphamide 4 g/m^2 plus G-CSF 5 μg/kg or G-CSF 10 μg/kg plus stem cell factor 25 μg/kg.[40] The target $CD34^+$ cell yield of 5×10^6/kg was obtained in 92% and 81% patients, respectively.[40] Thus, stem cell collection was slightly better in our previous experience, but this could be explained by differences in the priming. In the present study, stem cell collection was primed by G-CSF alone.

Bortezomib has already been tested as front-line therapy in candidates for ASCT. In a phase II study of bortezomib given as a single agent in patients with previously untreated MM, the CR rate was 11% and the PR rate 20%.[41] In another phase II trial, dexamethasone was added to bortezomib in 36 of 48 patients who failed to achieve PR after two cycles of treatment or CR after four cycles.[22,23] This addition led to 23 improved responses; the final rate of CR with negative immunofixation was 8%, and the overall CR rate (including near CR with positive immunofixation) was 19%, very similar to the CR rate we obtained in the current study with the same definition of CR.[22,23] However, in the current study, dexamethasone was administered from the start of the study and its use was not dependent on initial response to bortezomib. The combination of bortezomib with doxorubicin and dexamethasone (PAD) was evaluated in 21 patients. The overall CR rate after four cycles was 29% (including 24% CR with negative immunofixation), and the CR + VGPR rate was 62%.[39]

Thalidomide has also been used in combination with dexamethasone as induction therapy prior to ASCT. In a recently published study of 100 patients receiving this combination, the CR rate was 13% and the CR+VGPR rate was 19%.[34] In a randomized ECOG trial, the overall response rate was superior in the thalidomide + dexamethasone arm than in the dexamethasone-only arm.[38] However, the CR rate was only 4% in the combination arm. In these two studies, the use of thalidomide + dexamethasone was associated with important toxicities, including deep vein thrombosis (15% and 17%, respectively) and treatment-related death (5% and 4%, respectively). Bortezomib and thalidomide can also be combined with dexamethasone or chemotherapy. Preliminary results are encouraging with regard to stem cell mobilization and overall response rates,[42-43] but the possible added toxicity of this combination is not fully known.

Finally, lenalidomide was recently tested in combination with dexamethasone in 34 patients with newly diagnosed MM, and the CR+VGPR rate was 38%.[44] However, because this agent induces some degree of myelotoxicity, further evaluation is needed to assess its impact on stem cell collection. The use of lenalidomide in combination with dexamethasone is also associated with an increased risk of deep-vein trombosis.[45,46] Only prospective trials will be able demonstrate the value of using this agent as part of induction treatment prior to ASCT. In conclusion, the introduction of novel agents, such as bortezomib, to induction therapy should improve the CR+VGPR rate prior to ASCT. Although it has not been clearly demonstrated that response to induction therapy is related to final outcome, one can imagine that a higher initial efficacy could translate into a better result after ASCT and, finally, into longer survival. Another potential advantage would be to reduce the number of patients who need a second transplantation, since in the IFM 94 trial, only patients with less than a VGPR benefited from a second ASCT.[3] In this context, this phase II trial shows that the combination of bortezomib + dexamethasone is effective and well tolerated. It is too early to claim that it should replace VAD as induction therapy prior to ASCT, and assessment of survival data is required. However, these results justify a phase III randomized trial, which has just been initiated by the IFM, comparing this regimen with VAD.

JLH initiated the project, performed the update,analyses and wrote the manuscript; MA and PM supervised the project; HAL monitored the cytogenetic analyses and revised the manuscript; MA,XL,JT,BP,A-MS,CH,LB,J-GB,MR and PM included patients and reviewed the manuscript. The authors declare that they have no potential conflicts of interest.

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