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ORIGINAL ARTICLE

Bortezomib and dexamethasone as salvage therapy in patients with relapsed/refractory multiple myeloma: analysis of long-term clinical outcomes

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Abstract Bortezomib (bort)–dexamethasone (dex) is an effective therapy for relapsed/refractory (R/R) multiple myeloma (MM). This retrospective study investigated the combination of bort (1.3 mg/m^2 on days 1, 4, 8, and 11 every 3 weeks) and dex (20 mg on the day of and the day after bort) as salvage treatment in 85 patients with R/R MM after prior autologous stem cell transplantation or conventional chemotherapy. The median number of prior lines of therapy was 2. Eighty-seven percent of the patients had received immunomodulatory drugs included in some line of therapy before bort–dex. The median number of bort–dex cycles was 6, up to a maximum of 12 cycles. On an intention-to-treat basis, 55 % of the patients achieved at least partial response, including 19 % CR and 35 % achieved at least very good partial response. Median durations of response, time to next therapy and treatment-free interval were 8, 11.2, and 5.1 months, respectively. The most relevant adverse event was peripheral neuropathy, which occurred in 78 % of the patients (grade II, 38 %; grade III, 21 %) and led to treatment discontinuation in 6 %. With a median follow up of 22 months, median time to progression, progression-free survival (PFS) and overall survival (OS) were 8.9, 8.7, and 22 months, respectively. Prolonged PFS and OS were observed in patients achieving CR and receiving bort–dex a single line of prior therapy. Bort–dex was an effective salvage treatment for MM patients, particularly for those in first relapse.

Keywords Bortezomib · Multiple myeloma · Relapse · Treatment-free interval · Complete remission · Peripheral neuropathy

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Introduction

Despite major improvements in the prognosis of multiple myeloma (MM) that have been reported over the last decade with the progressive availability of the novel agents thalidomide, bortezomib, and lenalidomide, relapse eventually occurs in almost all patients [1, 2].

Bortezomib (bort) was the first proteasome inhibitor to be investigated both in preclinical and clinical studies in the relapsed/refractory (R/R) setting [3, 4]. In the two phase II Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy (SUMMIT) and Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma (CREST) trials, and the phase III Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial, which led to bort approval in R/R patients [5–7], this drug was investigated as a single agent. However, the addition of dexamethasone (dex) was permitted because of a suboptimal response to the first 2–4 cycles of therapy. In these studies, the response rate ranged from 30 to 50 %, median time to progression (TTP) was 6–7 months, and the one-year survival rate was in the 80 % range. However, in daily clinical practice, bort is more often combined with dex as salvage therapy for R/R MM.

The aim of the present analysis was to retrospectively evaluate the long-term outcomes of a cohort of 85 R/R MM patients treated with bort–dex.

Patients and methods

From 2004 to 2011, 85 patients with R/R MM were treated at our institution with bort at the dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 every 3 weeks in combination with dex at the dose of 20 mg on the day of and day after bort infusion. The treatment continued until achievement of best response or plateau phase, patients' tolerance, or disease progression, up to a maximum of 12 cycles. All patients were bort-naive. Informed consent was obtained from all patients.

Responses were assessed according to the European Group for Blood and Marrow Transplantation criteria [8], with the addition of two categories: near complete remission (nCR) (no evidence of M protein in serum and urine electrophoresis but immunofixation positive) and very good partial response (VGPR) (≥90 % reduction in serum M protein and less than 100 mg urine M protein per day). Progressive disease was defined as any of the following: increase of ≥25 % from baseline in serum or urine M protein (with an absolute increase of at least 0.5 g/dl and 200 mg/24 h, respectively, as compared with the nadir value), appearance of new osteolytic lesions or soft-tissue plasmacytomas (or definite increase in size of preexisting ones), and development of hypercalcemia (>11.5 mg/dl). Laboratory evaluations of efficacy were performed on the first day of every cycle.

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3. Treatment with bort was withheld from patients with ≥grade 3 non hematologic toxicity excluding peripheral neuropathy (PN) or grade 4 hematologic toxicity and then resumed at a 25 % reduced dose, provided that resolution or improvement to grade 2 or better was documented. Wherever PN developed, bort administration was modified as follows: no change for grade 1 sensory PN; dose reduction to 1.0 mg/m^2 for grade 1 neuropathic pain or grade 2 sensory PN; and for grade 2 neuropathy with pain or grade 3 sensory PN, bort was withheld until resolution of symptoms and then given at the dose of 0.7 mg/m^2 once weekly. Discontinuation of treatment was permanent in patients with grade 4 neuropathy.

Statistical analysis

Continuous data were expressed as median with interquartile range (IQR) or range. Discrete data were expressed as frequencies and percentage. The Kaplan–Meier method was used to estimate TTP (time from start of treatment with bort–dex to progression or relapse), progression-free survival (PFS; defined as time from start of treatment to progression or relapse, or death from any cause, whichever came first), and overall survival (OS; time from start of treatment to last follow up or death from any cause). Survival curves were compared using the log-rank test. Time to next treatment (TTnT) was calculated as time from the first dose of bortezomib to the start of a subsequent therapy while treatment-free interval (TFI) as time from the last administration of bort to the start of a subsequent therapy. The duration of response was calculated from the achievement of at least partial response (PR) to progression. Statistical analysis was performed using Stata v.11 and statistical significance was set at $p<0.05$. Cutoff data analysis was January 2013.

Results

The main characteristics of the 85 patients at the start of treatment are summarized in Table 1. Median age was 58 years (range, 36–77 years); 60 % of the patients were males. Seven

Table 1 Patient characteristics at the start of bort-dex treatment

N° patients	85
Male/Female	51/34
Median age (range) (years)	58 (36–77)
M protein isotype:	
IgG	44 (52 %)
IgA	26 (31 %)
IgD	2 (2 %)
BJ	9 (11 %)
NS	4 (4 %)
Durie–Salmon Stage:	
I	22 (26 %)
II	9 (11 %)
III	54 (63 %)
Median Hb (range) (g/dl)	10.9 (7.6–14.9)
Median PLT (range) (×10^3/mmc)	184 (18–459)
Median LDH (range) (U/l)	366 (141–2814)
Median calcium (range) (mg/dl)	9.2 (6.9–15.3)
Median creatinine (range) (mg/dl)	1 (0.5–8)
N° patients with ≥2 mg/dl	6 (7 %)
Extramedullary disease	11 (13 %)
Previous lines of therapy:	
1 line	28 (33 %)
2 lines	41 (48 %)
≥ 3 lines	16 (19 %)
Prior high-dose therapy ASCT	72 (85 %)
Prior IMiDs:	74 (87 %)
(Thalidomide/Lenalidomide)	(71/3)

BJ Bence Jones, *NS* not secretory, *Hb* hemoglobin, *PLT* platelets, *LDH* lactate dehydrogenase, *ASCT* autologous stem cell transplantation, *IMiDs* immunomodulatory drugs

percent of the patients had a serum creatinine level ≥2 mg/dl (median 1; range, 0.5–8 mg/dl), and 5 % presented with hypercalcemia (≥11 mg/dl). In 11 patients (13 %) extramedullary disease was present at the time of relapse.

The median number of prior treatment lines was 2 (range, 1–5): 28 patients (33 %) had previously received a single line of therapy, 41 (48 %) 2 lines, and 16 (19 %) ≥3 lines. First-line treatment included autologous stem cell transplantation (ASCT) in 72 patients (85 %) and standard-dose therapy in the remaining 13 patients. ASCT was given following induction with either thalidomide–dex (28 patients) or conventional chemotherapy (44 patients). Patients not treated with ASCT received upfront conventional chemotherapy (ten patients, 12 %) or melphalan–prednisone in association with thalidomide (two patients, 2 %) or lenalidomide (one patient). All in all, 74 patients had been exposed to immunomodulatory drugs (IMiDs) such as thalidomide (71 patients) or lenalidomide (3 patients) included in some prior line of treatment (87 %); three patients underwent allogenic stem cell transplantation, 65, 24, and 20 months, respectively, before starting bort–dex treatment (Table 1).

The median number of cycles of bort–dex actually received was 6 (range, 1–12); 8 % of patients received more than 9 cycles. Overall, median treatment duration was 4.1 (range, 0.3–13.1)months.

On an intention-to-treat basis, 47 patients (55 %) achieved at least PR, including 19 % CR, and 16 % nCR and VGPR (Table 2). Twenty percent of the patients maintained stable disease, while 25 % showed progression under treatment. The probability to achieve CR was 25 % for patients treated at first relapse and 16 % for those receiving two or more lines of prior therapy. No difference in terms of response was observed according to the presence or absence of extramedullary disease or renal failure at the time of starting bort–dex. The median time to best CR and at least PR was 3.3 and 2.2 months, respectively, and the median duration of response was 8 months each. The median TTnT was 11.2 months (IQR, 6.2–14.3) and the median TFI was 5.1 months (IQR, 1.4–11.2).

Table 2 Best response to treatment in the whole population and according to number of prior treatment lines

	All patients	1 line	≥2 lines
CR	16 (19 %)	7 (25 %)	9 (16 %)
nCR	6 (7 %)	1 (4 %)	5 (9 %)
VGPR	8 (9 %)	1 (4 %)	7 (12 %)
PR	17 (20 %)	7 (25 %)	10 (17 %)
MR/SD	17 (20 %)	4 (14 %)	13 (23 %)
PD	21 (25 %)	8 (29 %)	13 (23 %)

Response ≥VGPR: 35, 33, and 37 % in the whole population, 1 line and ≥2 lines, respectively; response ≥PR: 55, 58, and 54 %, respectively

CR complete remission, *nCR* near complete remission, *VGPR* very good partial response, *PR* partial response, *MR* minor response, *SD* stable disease, *PD* progressive disease

Twenty-nine per cent of the patients were retreated with bortezomib-containing regimens upon subsequent relapse, with an overall response rate of 58 % (≥46 % PR, ≥12 % VGPR, 4 % CR).

After a median follow-up of 22.0 months (IQR, 10.4–36.1), 70 patients had died, and 76 showed disease progression. Median TTP, PFS, and OS for the entire population were 8.9, 8.7, and 22 months, respectively. Attainment of high-quality responses significantly correlated with prolonged PFS and OS. In particular, PFS and OS for patients who achieved CR were 12.5 and 40.7 months, respectively, as compared to 6.5 and 19.5 months, respectively, for patients with less than CR (p=0.0005 and p=0.0059 for PFS and OS comparisons) (Fig. 1a, b).

Consistently, with the finding that less heavily pretreated patients achieved CR more frequently than those who had received at least two prior lines of therapy, PFS (1-year estimate, 39 %) and OS (median, 33.8 months) for the former group were significantly longer in comparison with patients previously exposed to ≥2 lines of treatment (PFS, 25 % at 1 year; p=0.0187; OS, 19.5 months median; p=0.0366) (Fig. 2a, b). Median survival after relapse from bort–dex therapy was 13 months.

The most common adverse events related to bort–dex were thrombocytopenia, gastrointestinal symptoms, and PN. Thrombocytopenia occurred in 40 patients, (grades 1–2, 6 %; grades 3–4, 41 %). Eight out of 17 patients with grade 4 thrombocytopenia received regular platelet support, while the others benefited from dose reduction of bort, leading to subsequent decrease in toxicity to grades 1–2. No major bleeding complications were reported.

Gastrointestinal symptoms (including diarrhea, nausea, constipation, and anorexia) were observed in 45 patients, were generally mild and well managed with routine support. Only three patients presented severe diarrhea requiring hospitalization; one patient discontinued treatment.

Sensory bort-induced PN (BiPN) occurred in 66 patients (78 %), with neuropathic pain in 30 cases and was of grade ≥2 in 59 % of them (38 % grade 2 and 21 % grade 3); no cases of grade 4 PN were observed. Of note, 35/66 patients with treatment-emergent neurological toxicity had preexisting grade 1 (23 patients) or grade 2 (12 patients) neuropathy at the time of starting bort–dex, mostly due to previous therapy with thalidomide. In 20 of these 35 (57 %) patients, PN worsened on bortezomib treatment, while it remained stable in the remaining 15 patients. The median time of onset of grade ≥2 PN was 87 (range, 25–199)days. PN led to bort dose reduction to 1 mg/m^2 in 34/66 patients (52 %), generally at cycle 4, and in 11 of these 34 patients a further dose reduction to 0.7 mg/m^2 was required, mainly at cycle 5. Five patients (6 %) permanently discontinued treatment due to painful grade 3 PN. Among 50 patients with grade ≥2 BiPN, 44

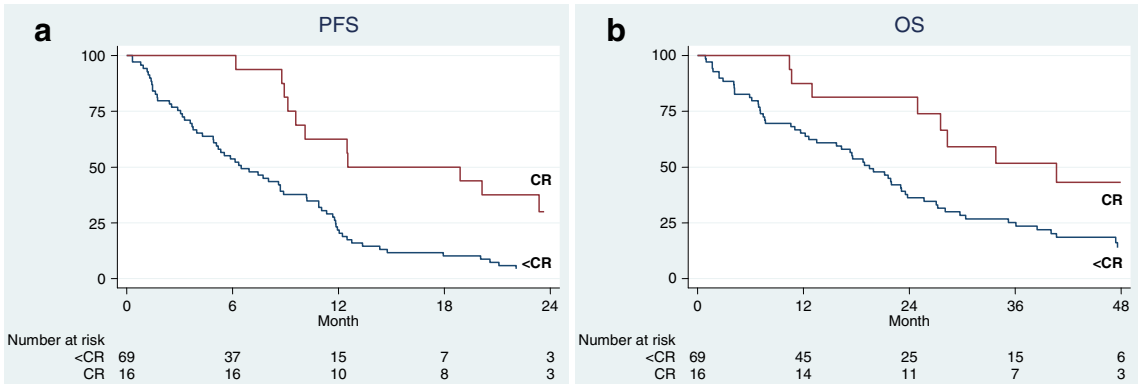

Fig. 1 PFS and OS according to the response to treatment (CR vs <CR). **a** PFS according to the response to treatment (CR vs <CR). **b** OS according to the response to treatment (CR vs <CR)

registered an improvement in neurological symptoms within a median time of 82 (range, 14–311)days. Improvement was achieved by appropriately reducing the dose of bort and using supportive therapy (gabapentin/amitriptyline and analgesics). In the remaining six cases, PN remained stable.

In all, a modification of the dose of bort to 1 mg/m^2 and to 0.7 mg/m^2 was required in 47 % (40/85) and 14 % (12/85) of patients, respectively; a total of six patients discontinued treatment due to severe adverse events. Patients who reduced the dose of bort at least once received a median number of treatment cycles significantly superior than patients who were ever treated with standard dose (7 vs 4, $p<0.001$). As a result, the median cumulative dose of bort was 33.2 mg/m^2 in the former group versus 20.8 mg/m^2 in the latter group ($p<0.001$). Moreover, a significant benefit with bort dose reduction was observed in terms of high-quality response rate (≥58 % vs 16 % VGPR, $p<0.001$), PFS (10 vs 5 months median, $p<0.001$) and OS (28 vs 16 months median, $p=0.04$).

Discussion

Bort was the first proteasome inhibitor to show high efficacy in R/R MM [9]. The phase III APEX trial designed to compare bort with high-dose dex demonstrated the superiority of single-agent bort, a finding that led to approval of the drug for R/R MM. The results of that study have been recently updated [10]. With an extended follow up of 22 months, the bort cohort showed an overall response and CR rate of 43 and 9 %, respectively; median TTP and OS were 6.2 and 29.8 months, respectively. In addition, a subanalysis performed according to the number of prior lines of therapy demonstrated a clinical benefit with bort used at first relapse vs more advanced phases of the disease [10].

The CREST and SUMMIT phase II studies in turn investigated single-agent bort at first relapse and in more heavily pretreated patients. In both studies, the addition of dex was allowed in patients with progressive disease after the first two cycles or stable disease after four cycles of bort treatment. The combination of bort and dex led to improved responses in 13/74 evaluable patients (18 %) in the SUMMIT study and in 9/27 (33 %) patients in the CREST study, without adversely affecting the safety profile of treatment [11]. Despite bort is usually given combined with dex, data reported so far in R/R MM are limited [12].

In our study of 85 patients, the observed rate of PR or better was consistent with that reported in other studies, but the frequency of CR was higher, up to the 19 % range.

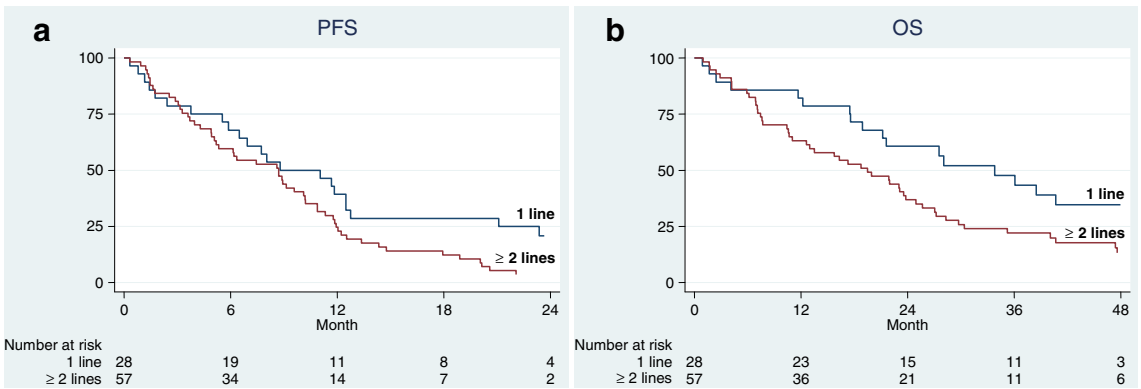

Fig. 2 PFS and OS according to number of prior treatment lines (1vs ≥2). **a** PFS according to number of prior treatment lines (1 vs ≥2). **b** OS according to number of prior treatment lines (1 vs ≥2)

Achievement of high-quality responses, including CR and at least VGPR, is generally recognized as a major prognostic factor for both newly diagnosed and R/R MM patients. We confirmed the close relationship between high-quality responses and outcomes, PFS and OS being significantly longer for patients achieving CR than for those who failed this goal (PFS, 12.5 vs 6.5 months median and OS, 40.7 vs 19.5 months median, respectively). In addition, a significant clinical benefit was also observed with the use of bort–dex at the time of first relapse. In particular, median PFS and OS proved longer for patients treated with bort–dex after a single line of prior therapy versus those who had received multiple lines of therapy (PFS at 1 year, 39 vs 25 %; OS, 34 vs 19.5 months median, respectively).

The high percentage of patients receiving IMiDs (84 %) before bort treatment precluded a sub-analysis aimed at exploring the impact of different classes of novel agents on the efficacy of bort–dex as salvage therapy for R/R MM. Thus, our analysis basically reflects the outcome of a population of patients receiving bort–dex after prior line(s) of treatment including thalidomide.

Twenty-nine percent of patients received re-treatment with bort at subsequent relapse, and attained an overall response rate (ORR) of 58 % (46 % ≥PR, 4 % CR), which is in line with several reports on the efficacy of bort re-treatment [13, 14].

Concerning the safety profile of bort–dex, PN was the most clinically relevant and frequently observed adverse event, requiring dose modifications in 52 % of the patients. In our analysis, we observed a 59 % incidence of ≥grade 2 or higher and 21 % of grade 3 PN, values higher than previously reported [5, 12]. This finding could partly be explained by the high rate of patients with preexisting PN, mostly thalidomide-induced. Nevertheless, only five patients required bort treatment discontinuation, while improvement or resolution of PN was observed in the majority of patients. Among these latter, the probability to improve/resolve PN and time to achieve this objective were consistent with other reports [15]. Means to further reduce the incidence of BiPN could include modifications of bort schedule from twice-weekly to once-weekly infusions [16] or the use of subcutaneous administration of the drug, which was recently reported to be as effective as the intravenous delivery and to reduce the rates and severity of PN [17].

Other adverse events, including gastrointestinal symptoms, thrombocytopenia, and fatigue, were generally mild, manageable, and reversible.

Despite a subgroup of patients who required a dose reduction of bort due to adverse events, they actually received a higher number of treatment cycles and a higher cumulative dose of bort, that ultimately resulted in improved response rate, PFS and OS in comparison with patients treated with full dose therapy. Changes in bort dosing and schedule can improve the feasibility of treatment, leading to prolonged therapy and thus a better outcome [18, 19].

In an attempt to overcome emerging resistance to bort and improve the safety profile of this agent, novel proteasome inhibitors have been recently explored. Carfilzomib is a second generation proteasome inhibitor that proved promising and of lasting effect both in preclinical studies and in phase I/II studies in R/R MM, either as single agent or in combination with IMiDs or panobinostat [20, 21]. Although up to 70 % of patients were refractory to bortezomib or IMiDs at enrollment in these studies, carfilzomib was reported to affect an ORR ranging from 17 to 59 %, with a DOR of 7.2 to 10.6 months, and very low rates of PN. More recently, the novel oral proteasome inhibitor MLN9708 has shown potent in vitro and in vivo anti-MM activity, both as a single agent and in combination with IMiDs, steroids, or histone-deacetylase inhibitors [21, 22]. MLN9708 is currently being investigated in phase I–III studies, both in the R/R setting and in previously untreated patients.

In conclusion, bort–dex was shown to be an effective salvage therapy for R/R MM, affecting a high rate of CR and long-lasting clinical benefit, particularly for patients treated at first relapse and those achieving CR.

Disclosures Prof. Michele Cavo has received honoraria and has been a member of the advisory board for Celgene, Jansen-Cilag and Novartis. All the other authors declare no relevant competing financial interests. The work had no specific funding. Informed consent was obtained from all patients.

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