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BORTEZOMIB IN MULTIPLE MYELOMA: TREATMENT AND RETREATMENT. A SINGLE CENTER EXPERIENCE

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The proteasome inhibitor bortezomib (Velcade, formerly PS-341) induces apoptosis, reverses drug resistance of multiple myeloma (MM) cells, and affects their micro- environment by blocking cytokine circuits, cell adhesion and angiogenesis. It shows encouraging results in patients with relapsed and newly recognized MM (1-4). *In vitro* bortezomib demonstrates potent synergy with cytotoxics including anthracyclines (5-7). In previously untreated patients with MM PAD combination therapy (bortezomib, doxorubicin, dexamethasone) gives responses in 95% of patients (8). Some reports in abstract forms have suggested that bortezomib is effective in inducing responses in patients with primary or secondary plasma cell leukemia (PCL) (9, 10).

The aim of the present study was to evaluate the efficacy and safety of bortezomib alone and in combination with doxorubicin and dexamethasone in the treatment and retreatment of relapsed MM and its aggressive variant – PCL.

EXPERIMENTAL

Four patients with PCL and 25 patients with relapsed MM who have failed at least two prior lines of treatment, including 4 patients treated with high dose therapy and autologous stem cell transplantation, were treated with bortezomib at the Department of Hematology of the Institute of Hematology and Transfusion Medicine in Warsaw. Patients characteristics are presented in Table 1. Bortezomib (Velcade®; Millennium Pharmaceuticals, Janssen – Cilag) was administered intravenously at a dose of 1.3 mg/m^2 on days 1, 4, 8 and 11 in a 21-day cycle for a total of six cycles. In 11 patients doxorubicin 9 mg/m^2 and dexamethasone 40 mg on days 1-4 were added to the regimen (= PAD regimen) (8) and in 2 patients with disease sensitive to the bortezomib therapy, bortezomib was re-administered in the consecutive relapses.

The primary end point of the study was response rates. Secondary efficacy parameters included progression free survival and time to progression. Safety and toxicity were also secondary objectives of the study. Responses were assessed according to IMWG criteria (11). Near complete response (nCR) was defined as the absence of monoclonal immunoglobulin (M-protein) in the serum and urine determined by electrophoresis but with positive immunofixation, plus stable bone disease and normal serum calcium.

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, Version 2.0). For treatment efficacy evaluation there were taken into account only those patients who received at least 3 cycles of bortezomib therapy.

All patients gave written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki; the approval was obtained from the local Institute Bioethics Commission.

RESULTS

Partial response (PR) was achieved in 4 of 13 (30%) evaluated MM patients treated with bortezomib alone (Table 2). The median duration of response was 6 months. The median time to progression of disease was 7 months. In one case of recurrent MM who was three times treated with bortezomib, with preserving a 18-month break interval between first and second and 8 months between second and third therapy courses, all three treatments resulted in achieving nCR which lasted each 6 months. The patient, 122 months since MM diagnosis, feels good.

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Of 3 assessed patients (2 PCL, 1 MM) treated with bortezomib acc. to PAD regimen in second line therapy, after low-effective treatment with VAD, nCR was achieved in one and PR in two patients.

In the patient with primary PCL and nCR achieved subsequent to induction PAD treatment, following cyclophosphamide peripheral blood stem cells were successfully harvested and autologous peripheral blood stem cell transplantation (PBSCT) was performed. Time to neutrophil > 0.5×10^6 engraftment was 20 days and time to platelet > 20×10^6 engraftment was 17 days. PBSCT led to complete remission which lasted 7 months. Partial remission was achieved subsequently to relapse retreatment with PAD. At present, the patient in partial second remission, 23 months after diagnosis of PCL, feels good but cannot walk because of peripheral grade 3 sensory neuropathy.

In the second primary PCL patient with thrombocytopenia and terminal kidney failure on dialyses, 6 PAD cycles resulted in partial remission. After 12 months since PCL diagnosis the patient feels good, dialyses are continued.

Among evaluated 2 patients – one with PCL recurrence and the other one with MM relapse – PAD therapy resulted in partial response in the first one while the other patient did not respond to treatment.

Table 1. Baseline patient's characteristics and disease features

Characteristic	Bortezomib alone N = 18	PAD N = 11
Age,years, median (range)	61 (39-70)	57 (46-71)
Gender (%) Male/Female	7/11 (39/61)	6/5 (55/45)
M-protein isotype (N) IgG [(κ : λ)] IgA [(κ : λ)] Light chain [(κ : λ)]	15 (10:5) 2 (2 : 0) 1 (0 : 1)	8 (3:5) 1 (1:0) 2 (1:1)
ISS (12) stage of disease I/II/III, %	50, 44, 6	55, 18, 27
β_2M < 2.5 /2.5-5.5/> 5.5 mg/L, % (median β_2M, mg/L)	44/50/ 6 (2.6)	27/46/27 (2.9)
Albumin < 3.5 g/dL, % (median albumin, g/dL)	16 (3.9)	27 (3.8)
Median bone marrow plasma cells, %	34	20
Lytic bone lesions, %	77	82
Durie Salmon Staging (%) I A IIA III A III B	 22 11 62 5	 10 45 45
Median time since multiple myeloma diagnosis to onset of bortezomib therapy (months)	44	11
Prior therapy (N) MP CP VMCP VBAP VAD CTD Thalidomide EDAP	 4 2 3 2 6 8 1	 2 2 2 2 5 1
Autologous stem cell transplantation	3	1
Radiation therapy	3	2
Number of prior regimens of treatment	2.4 (1-5)	1.3 (1-2)

Abbreviations: MP, melphalan, prednisone; CP, cyclophosphamide, prednisone; VMCP, vincristine, melphalan, cyclophosphamide, prednisone; VBAP, vincristine, carmustine, adriamycin, prednisone; VAD, vincristine, adriamycin, dexamethasone; CTD, cyclophosphamide, thalidomide, dexamethasone; EDAP, etopozide, dexamethasone, cytosine arabinoside, cisplatin; ISS, International Staging System.

Table 2. Overall response rates to bortezomib alone and PAD (N = 29)

	Response							
	Bortezomib				PAD			
	N (evaluable)	nCR	PR	> PR%	N (evaluable)	nCR	PR	>PR%
Multiple myeloma								
Second line induction therapy					5 (1)		1	100
Relapse	18 (13)	1	3	30	3 (1)			0
PCL								
Second line induction therapy					2 (2)	1	1	100
Recurrent	1			0	2		1	50
Salvage therapy	(1)				(2)			

Abbreviations: PAD, bortezomib, doxorubicin, dexamethasone; nCR, near complete response; PR, partial response; PCL, plasma cell leukemia.

Table 3. Adverse events during bortezomib treatment

Event	No. of patients receiving bortezomib alone (N = 18)	No. of patients receiving PAD (N = 11)
Anorexia	2	2
Nausea / Vomiting	2	1
Fatigue	7	3
Hypotension	4	1
Infection	5	6
Pyrexia	8	5
Peripheral neuropathy	8	3
Paresthesia	6	2
Insomnia	2	
Rash/erythema multiforme	3	1
Local erythema in site of bortezomib i.v. infection	2	
Abdominal pain	4	3
Subileus	1	2
Cerebral multiple embolisms	1	
Bone pain	2	1
Pain in limb	3	1
Anemia	4	4
Neutropenia	3	3
Thrombocytopenia	6	4
Mild hipertransaminasemia	3	2
Hiperkalemia	2	
Herpes zoster	2	2
Hipokalemia		1

Treatment with bortezomib was discontinued in 6 patients (20%) (after 1,2,3,3, 4 and 5 cycles, respectively) because of skin lesions (erythema multiforme), subileus, aggravation of peripheral neuropathy and progression of disease. Side effects seen in the study included also herpers zoster in 4 patients, pyrexia, infections, nausea, vomiting abdominal pain, pain in limbs, hypotension, thrombocytopenia (Table 3). Overall, 38% of patients developed neuropathy, which was grade 1 in all except two patients. In two patients treated with PAD regimen grade 3 febrile neutropenia and thrombocytopenia were observed.

DISCUSSION

In the current study only four of 13 evaluable relapsed MM patients achieved partial response after treatment with bortezomib alone. The median duration of the response was 6 months. The median time to progression of disease in all 13 patients receiving bortezomib alone was 7 months. Similarly, in phase II multicenter trial SUMMIT, the response rate on bortezomib alone was 27% and the median time to progression of disease among all 202 patients with recurrent and refractory MM was 7 months (1). In APEX study, an international, randomized phase III trial, which was performed to compare the efficacy of bortezomib with dexamethasone in the treatment of relapsed MM, the response rates were 38% for bortezomib and 18% for dexamethasone. The median duration of the response was 8 months in the bortezomib group and 5.6 months in the dexamethasone group. Median

times to progression in the bortezomib and dexamethasone groups were 6.22 months and 3.49 months, respectively (2).

In one our heavily pretreated relapsed MM patient triple remission after bortezomib therapy was achieved. A retrospective analysis of material from basic studies SUMMIT, CREST and APEX shows that 11 of 22 MM patients who received again bortezomib, as a component of combined therapy, responded to this treatment (1, 2, 13). Also other analyses published in abstract form suggest the efficacy of bortezomib retreatment (14-16).

PAD (PS – 341/ bortezomib, doxorubicin and dexamethasone) combination therapy was reported to be highly effective regimen as an induction therapy before high dose therapy in newly diagnosed MM patients (8). In our study PAD induction regimen was used prior to high dose therapy with PBSCT rescue in one patient with primary PCL. It was found that stem cell mobilization was not impaired and the patient regenerated neutrophils and platelets on days 20 and 17, respectively, confirming the quality of stem cell harvest. Also *in vitro* data suggested that the combination of bortezomib, doxorubicin and dexamethasone showed very little synergy in inhibiting the proliferation of normal CD34-selected cells from blood or marrow (5). In our patient with primary PCL complete remission was achieved with PAD and ASCT which lasted 7 months. PAD re-induction therapy was used for an above-mentioned PCL patient previously sensitive to such a treatment and then relapsing post autologous transplant. Partial response was achieved with PAD retreatment. Morris et al. (17) found that PAD given at MM relapse following autologous transplant is significantly more effective than VAD or VAD-like therapy used as induction therapy. Similarly, Lee et al. (18) reported that PAD therapy followed by thalidomide and dexamethasone combination therapy in patients with relapsed MM is very active and tolerable.

In the current study the major side effects of bortezomib were consistent in type and frequency with those described previously (1-3). The most serious adverse events observed in our study were peripheral neuropathy, subileus, hypotension, herper zoster and thrombocytopenia (Table 3). Five patients had adverse events necessitating early discontinuation of treatment, three patients experienced worsening of peripheral neuropathy, one developed erythema multiforme and one had subileus and ischemic cerebral apoplexy (brain CT revealed multiple embolisms within frontal, parietal and left occipital lobes).

CONCLUSIONS

In relapsed MM the rate of response to bortezomib alone is 30 percent, with median duration of response of 6 months. Presented here cases demonstrate the efficacy of repeated bortezomib treatments in the patients with recurrence of myeloma who were previously sensitive to such a treatment. We suggest, bortezomib in combination with other agents may be considered as an intial treatment of primary PCL. PAD regimen is effective and dose not prejudice peripheral blood stem cell collection or subsequent engraftment.

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