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Bortezomib (Velcade) for progressive myeloma after autologous stem cell transplantation and thalidomide

Pellegrino Musto [a,*], Antonietta Falcone [a], Grazia Sanpaolo [a], Tommasina Guglielmelli [b], Renato Zambello [c], Enrico Balleari [d], Lucio Catalano [e], Mauro Spriano [f], Federica Cavallo [g], Antonio La Sala [a], Saverio Mantuano [a], Michele Nobile [a], Lorella Melillo [a], Potito Rosario Scalzulli [a], Matteo Dell'Olio [a], Carlo Bodenizza [a], Michele Mario Greco [a], Angelo Michele Carella Jr. [a], Emanuela Merla [a], Angelo Michele Carella [f], Mario Boccadoro [g], Nicola Cascavilla [a], Antonio Palumbo [g]

[a] *Unit of Hematology and Stem Cell Transplantation, IRCCS "Casa Sollievo della Sofferenza" Hospital, S. Giovanni Rotondo, Italy*
[b] *Hematology Unit, "S. Luigi Gonzaga" Hospital, Orbassano, Italy*
[c] *Department of Clinical and Experimental Medicine, University of Padova, Italy*
[d] *Department of Internal Medicine, University of Genova, Italy*
[e] *"Federico II" University, Napoli, Italy*
[f] *Hematology Unit, "S. Martino" Hospital, Genova, Italy*
[g] *University of Torino, Italy*

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Abstract

Twenty-one patients with multiple myeloma, all relapsed after frontline autologous stem cell transplantation and all relapsed again after or resistant to thalidomide (employed as second line treatment) received bortezomib (1.3 mg/m^2 body surface twice weekly for 2 weeks followed by an interval of 10–12 days) without adjunct of steroids as third line therapy. Three patients died of progressive disease during the first 2 cycles with bortezomib. Eighteen patients received at least 2 cycles and were evaluated for response. According to EBMT criteria, two complete (negative immunofixation) and seven partial (reduction of M-component > 50–75%) remissions were achieved (ITT response rate 42.8%). Duration of response lasted from 2 to 14+ months. Grades 3–4 toxicities (thrombocytopenia, leucopenia, peripheral neuropathy and vasculitis) were observed in seven patients, but no patient interrupted the treatment due to side effects. We conclude that bortezomib alone may induce high quality responses as third line salvage therapy with acceptable toxicity in a significant proportion of homogeneously pre-treated myeloma patients with progressive disease after autologous transplantation and thalidomide.

Keywords: Bortezomib; Multiple myeloma; Autologous stem cell transplantation; Thalidomide; Relapse; Salvage therapy

1. Introduction

Single or tandem autologous stem cell transplantation (AuSCT) is extensively used as front-line therapy in multiple myeloma (MM) [1–3]. Thalidomide, in combination with dexamethasone, is highly effective for patients who relapse after AuSCT [4–7]. Despite the initial efficacy of these therapies, however, relapse is invariably the rule. A further optimal therapeutic choice remains undefined in these patients.

Bortezomib (VELCADE, formerly PS-341, Millennium, USA), is a novel first-class agent that inhibits the proteasome, a multicatalytic cellular enzyme whose activity entails several molecular mechanisms, including, in particular, the NF-kB pathway [8]. In phase 1–2 studies [9–11], as well as in community centers compassionate need programs [12,13],

* Corresponding author. Tel.: +39 0 882 411389; fax: +39 0 882 410258.
E-mail address: p.musto@tin.it (P. Musto).

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bortezomib was effective as single agent in 35–38% (and up to 50%, when dexametasone was added) of patients with advanced MM. In a recently published phase 3 trial, bortezomib did significantly better than dexamethasone as salvage treatment in MM in terms of response rate, time to progression and survival benefits [14]. Currently, bortezomib, alone or in combination with dexamethasone and doxorubicin, is under investigation as first-line and maintenance therapy, with initial trials demonstrating an overall response rate of about 90%, a substantial proportion of complete or near-complete remissions and the possibility of adequate collections of peripheral blood stem cells [15,16].

However, in previous studies on advanced disease, the prior regimens were highly heterogeneous, their median number ranged from 2 [14] to 6 [10], some patients received up to 15 lines of therapy before bortezomib [10]. Therefore, in order to obtain more careful informations about the efficacy and tolerability of this drug in more homogeneously and less heavily pre-treated patients, we focused on the effects of bortezomib on a selected cohort of MM patients who had progressive disease after previous treatments including exclusively AuSCT and thalidomide.

2. Patients and methods

Within a multi-institutional italian series of 49 patients with advanced MM treated with bortezomib on a compassionate basis outside of clinical trials [13], 21 subjects were retrospectively selected for this study (males 13, females 8; mean age 58, range 41–67; IgG 16, IgA 5; clinical stage: IIA 4, IIIA 16, IIIB 1).

All patients had received AuSCT as first line treatment (Table 1). In general, they had been previously treated with 2–6 cycles of VAD or VAD-modified regimens as debulking treatment, followed by 1–2 mobilizing therapies with high dose cyclophosphamide plus G-CSF. Intermediate-high doses melphalan alone or in combination with TBI were the conditioning regimens applied. After a first relapse following AuSCT, all patients had received thalidomide (100–200 mg/day p.o.), alone or in combination with dexamethasone (40 mg/day p.o. or i.v. for 4 days every 4 weeks), as first salvage therapy (Table 1). After thalidomide, fifteen patients had relapsed and six had resulted resistant to this treatment. The majority of patients had also received zoledronic acid (4 mg every 4 weeks), while eleven patients had undergone local radiotherapy. In all these 21 patients, bortezomib was homogeneously given as third line treatment (second salvage therapy, Table 1).

Bortezomib was used on a compassionate basis, as single agent, at the dose of 1.3 mg/m^2 body surface twice weekly for 2 weeks (1 cycle), followed by 10–12 days without treatment. The dose and the intervals were modulated according to the manufacturer instructions in the presence of relevant toxicities. Written informed consent and approval by local Ethical Committees were achieved in all patients.

Table 1
Treatments and results in myeloma patients receiving bortezomib as third line therapy after AuSCT (first line) and thalidomide (second line)

First line therapy	
Single/double AuSCT: 9/12	
Conditioning regimens: Mel 100/Mel 200/Mel 140 + TBI: 7/12/2	
CR/PR after AuSCT: 5/16	
Duration of response (median, range): 23 months (4–41)	
Second line therapy	
Thalidomide alone/plus dexamethasone: 7/14	
Thalidomide dose 100/200 mg/day: 10/11	
PR/NR after thalidomide: 14/7	
Duration of response (median, range): 9 months (0–19)	
Third line chemotherapy	
Bortezomib 1.3 mg/m^2 d 1, 4, 8, 11	
CR/PR/NR after bortezomib: 2/7/12	
Duration of response (median, range): 7 months (2–14+)	

AuSCT: Autologous Stem Cell Transplantation; Mel 100, 200, 140: Melphalan 100, 200, 140 mg/m^2; TBI: total body irradiation; CR: complete remission; PR: partial remission; NR: no response.

3. Results

A total number of 71 cycles was administered (median 3, range 0.5–8 per patient). Three patients died of progressive disease during the first 2 cycles with bortezomib. Eighteen patients received at least 2 cycles and were evaluated for response. Relevant adverse events are reported in Table 2. Grades 3–4 WHO toxicities (thrombocytopenia, neuropathy, leucopenia, leucocytoclastic vasculits diagnosed by skin biopsy) occurred in seven patients, determining the need of reducing or temporarily stopping the treatment.

According to EBMT criteria [17], two patients achieved complete remission (CR) with negative immunofixation in serum and urine, while seven patients obtained partial remissions (PR) (reduction of M-component >75% in two cases, >50% in the other five patients) (Table 2). Of interest, three responders to bortezomib had obtained no benefit by thalidomide at first relapse. The remaining twelve patients had no

Table 2
Adverse events occurring during bortezomib therapy, according to World Health Organization (WHO) criteria

	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia	6	4	2	2
Leucopenia	3	3	1	
Anemia	1	1		
Fatigue	2	2		
Nausea/vomiting	1			
Bone pain/arthralgias	2	4		
Peripheral neuropathy	3	2	1	
Constipation	3	2		
Infectious episodes		2		
Diarrhoea	1	1		
Cutaneous vasculitis			1	

response or progressive disease and interrupted the treatment after 2–3 cycles. Overall, intention-to-treat response rate was 42.8%. Duration of response ranged form 2 to 14+ months. In two responders, a program of unrelated, non-myeloablative stem cell transplantation was started. In responders, the median value of bone marrow plasma-cell infiltration reduced from 52% (range 15–95%) to16% (range <1–25%). Responding patients also showed significant evidence of improved hemoglobin levels, performance status, quality-of-life and levels of normal immunoglobulins (data not shown). Bortezomib normalized renal function in one patient with a moderate increase of serum creatinine (2.2 g/dl). At present time, fourteen patients are alive with a median follow-up of 13 months (range 2–26 months).

4. Discussion

Knowing which strategies offer the best therapeutic chances after initial treatments in MM patients is mandatory, as quality of life and survival are significantly affected by salvage therapies. Bortezomib has been demonstrated to be an effective option for MM patients with advanced disease [9–14]. However, available published studies included a mixture of patients with multiple and heterogeneous previous regimens. Here, we focused on the effects of bortezomib as third line treatment (second salvage therapy) in a very homogeneous group of MM patients induced by AuSCT and relapsed or refractory after thalidomide employed as second line treatment (first salvage therapy).

Our study indicates that the use of bortezomib, in this specific setting, is generally safe and may be effective in a relevant proportion of cases. Responses, when occur, are qualitatively relevant, sometimes durable and may allow to take time for possible following additional approaches, such as allogeneic transplantation. If the proportion of responders in these patients may be further increased by adding dexamethasone to bortezomib is currently under investigation. Of particular interest, bortezomib was effective in some patients in whom thalidomide had failed. This confirms that the combination or the use in sequence of bortezomib and thalidomide (or its less toxic and more potent derivates, such as lenalidomide) could be particularly useful in MM patients.

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