Bortezomib as an Alternative in the Treatment of Patients With Malignant Gammopathy

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Abstract

Objective: To describe the use of bortezomib in a district hospital as an alternative in the treatment of malignant gammopathy.
Methods: A retrospective analysis was carried out on patients treated with bortezomib in our hospital between November 2005 and October 2007. The patients' medical histories were used to obtain data regarding diagnosis, treatments prior to bortezomib, date of the last disease progression, number of bortezomib courses, response to bortezomib, overall and event free survival, complications, and side effects.
Results: Forty-seven percent of the patients studied were male (5/12). The median age was 67, (range, 40-81). The main diagnosis was multiple myeloma on its own or associated with plasmocytoma. Bortezomib initiation coincided with the last disease progression in 83% of patients (10/12). Fifty percent of the patients completed 7-8 courses of bortezomib. Response was seen in 58% of the patients (7/12), partial response in 33% of them (4/12), and complete response in 25% (3/12). The most common adverse reactions were neuropathy and gastrointestinal toxicity which required treatment to be discontinued in 50% of cases.
Conclusions: According to the results obtained, bortezomib is a good alternative in the treatment of malignant gammopathy, above all in the case of plasmocytomas.

Key words: Multiple myeloma. Bortezomib. Efficacy. Safety.

Bortezomib como alternativa en el tratamiento de pacientes con gammapatías malignas

Objetivo: Describir el uso de bortezomib en un hospital comarcal como alternativa en el tratamiento de gammapatías malignas.
Métodos: Análisis retrospectivo de los pacientes tratados con bortezomib en nuestro hospital desde noviembre de 2005 hasta octubre de 2007. A partir de la revisión de las historias clínicas de los pacientes se recogieron los datos correspondientes al diagnóstico, tratamientos previos a bortezomib, fecha de la última progresión de la enfermedad, número de ciclos de bortezomib, respuesta a éste, supervivencia global y libre de progresión, complicaciones y efectos secundarios.
Resultados: El 47% de los pacientes estudiados eran varones (5/12), con una mediana de edad de 67 años (rango, 40-81 años). El diagnóstico principal fue mieloma múltiple, solo o asociado a plasmocitoma.
El inicio con bortezomib coincidió con la última progresión de la enfermedad en el 83% de los pacientes (10/12). El 50% completó 7-8 ciclos con bortezomib. Se obtuvo respuesta en el 58% de los pacientes (7/12), alcanzándose criterios de respuesta parcial en el 33% (4/12) y respuesta completa en el 25% (3/12). Las reacciones adversas más frecuentes fueron neuropatía y toxicidad gastrointestinal, y supuso la suspensión del tratamiento en el 50% de los casos.
Conclusiones: Según los resultados obtenidos, bortezomib es una buena alternativa en el tratamiento de las gammapatías malignas, sobre todo en el caso de plasmocitomas.

Palabras clave: Mieloma múltiple. Bortezomib. Eficacia. Seguridad.

INTRODUCTION

Multiple myeloma (MM) is the second most frequent haematologic neoplasia after lymphomas. In Spain, incidence is 4 out of every 100 000 persons per year. Currently, both incidence and mortality of this disease are increasing due to new technologies in diagnosis and the aging population.[1] Before the availability of chemotherapy

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treatment, average survival was 7 months, but with chemotherapy, prognosis increased significantly (average survival, 24-30 months).[2] In recent decades, new therapeutic strategies have developed for treating myeloma, such as haematopoietic progenitor cells transplantation, immunomodulator drugs (thalidomide, lenalidomide), and proteasome inhibitors (bortezomib). These advances have led to better disease control and survival, along with an improved quality of life for myeloma patients.[3]

Bortezomib is a reversible inhibitor of proteasome which has shown to be substantially active against multiple tumours, including MM. Its mechanism of action is to specifically inhibit chymotrypsin activity of the 26 S proteasome of mammal cells.[4] A consequence of proteasome inhibition by bortezomib is the accumulation of a NFκB inhibitor (nuclear factor kappa B). In the cell, this factor's inhibition allows for a decrease of the expression of adhesion molecules and of various factors of growth, survival, and angiogenesis, leading to an increase of protein values which promote myeloma cell apoptosis, along with other mechanisms.[5]

The only indication approved for bortezomib since its commercialization on April 26, 2004 is its treatment for progressive MM, as a monotherapy for patients who have previously received at least one treatment and have undergone or are not candidates for a bone marrow transplant.[4] Furthermore, this indication is used for plasmocytoma treatment,[6] plasma cell leukaemia,[7] and non-hodgkin lymphoma treatment[8] as compassionate use.

The objective of this study was to describe bortezomib as an alternative for malignant gammopathy treatment in terms of safety and efficacy in a district hospital.

METHOD

A retrospective study was carried out on haematological patients who were prescribed bortezomib in a district hospital from November 2005 to October 2007.

The parameters collected from patients' clinical records and from the cytostatic database of the pharmacy department were: age at initiation of bortezomib treatment; sex; diagnosis and date; previous treatments; date of the last disease progression; initiation of bortezomib treatment (by itself or combined treatment); number of bortezomib courses; response to bortezomib; overall and event free survival; complications, and adverse reactions.

Diagnostic criteria used were bone marrow plasma cells with more than a 10% presence or presence of one or more plasmacytomas, plus one of the following criteria: monoclonal component >30 g/L or presence of light chains in urine or osteolytic lesions not attributable to any other cause.[9] To evaluate response to treatment, the following criteria were defined[10]:

– Complete response: absence of monoclonal immunoglobulin (M protein) in serum and urine confirmed by immunofixation, <5% of bone marrow plasma cells and with no changes in the shape or number of bone lesions
– Partial response: at least a 50% reduction of serum M protein and its reduction in urine of at least 90%, reduction of bone marrow plasma cells ≥50% (in non-secreting myeloma patients) and with no changes in the shape or number of bone lesions
– Minimum response: a 25% to 49% reduction of M protein in serum and a reduction in urine from 50% to 89%, reduction of bone marrow plasma cells from 25% to 49% (in non-secreting myeloma patients) and with no changes in the shape or number of bone lesions
– Stable disease: no minimal response criteria are found or disease progression
– Disease progression: an increase of serum or M protein in urine of more than 25%, an increase of bone marrow plasma cells of more than 25%, new or increased bone lesions, or plasmocytomas

For plasmocytomas, a partial response to treatment was considered in case there was a reduced mass, and complete response was considered in case there was complete plasmocytoma fusion.

Adverse reactions or complications were registered according to patients' clinical history and were considered to be related or possibly related to bortezomib treatment. Clinical seriousness was evaluated based on *Common terminology criteria for adverse events* (CTCAE).[11]

RESULTS

A total of 12 patients were studied who were treated with bortezomib. Of all patients, 42% were males (5/12) and 58% females (7/12), with a median age of 67 years (range, 40-81 years). The majority of patients were diagnosed with only MM or MM associated with medullary plasmocytoma. Only 1 patient was diagnosed with solitary plasmocytoma (right maxillary plasmocytoma) and another patient with plasma cell leukaemia. Bortezomib was used in these 2 patients as a first line treatment and compassionate use.

Diagnosis and previous treatments for patients is shown in Table 1.

The median time from disease diagnosis to initiation of bortezomib treatment was 24 months, and there was high variability if patients were evaluated individually (range, 0-18 years). This initiation, except in patients 4 and 5, coincided with the last disease progression. All patients began bortezomib with a 1.3 mg/m^2 dose on days 1, 4, 8, and 11, by itself or combined with dexamethasone, except for patient 4, who began bortezomib combined with doxorubicin and dexamethasone (BAD).

Of the 12 patients included in the study, only 6 completed 7-8 courses of bortezomib. Partial response was reached in 3 patients diagnosed with MM (patients 1, 3, and 7); complete response was reached in 2 with MM associated with plasmocytoma (patients 2 and 8) because of complete disappearance of the plasmocytoma, and only 1 patient had no response after 8 courses of bortezomib (patient 11). For this patient, third line chemotherapy treatment was initiated with cyclophosphamide, bortezomib, and

Table 1. Diagnosis and Treatment of Patients Studied

Patient	Diagnosis	Previous Treatment
1	MM IgG κ	MP, VBCMP/VBAD (3 courses)
2	MM IgG κ + Pl	VBCMP/VBAD (3 courses), radiotherapy, HPCT, D
3	MM IgG κ	MP, CVMP, thalidomide
4	PCL	–
5	Solitary P	–
6	MM IgA κ	MP, VAD (6 courses)
7	MM IgG κ	MP, cyclophosphamide, D
8	MM IgG κ + Pl	CVMP, CVMP + biphosphonate
9	MM IgA κ	VBCMP/VBAD, P + biphosphonate, 2 HPCT
10	MM IgG κ + Pl	MP, VBCMP/VBAD, HPCT, P + biphosphonates
11	MM IgG κ	VAD
12	MM IgA κ	VAD, HPCT

CVMP indicates cyclophosphamide, vincristine, melphalan, and prednisone; D, dexamethasone; HPCT, haematopoietic cells transplantation; MM, multiple myeloma; MP, melphalan and prednisone; PCL, plasma cell leukaemia; Pl, plasmocytoma; VAD, vincristine, doxorubicin, and dexamethasone; VBAD, vincristine, carmustine, doxorubicin, and dexamethasone; VBCMP, vincristine, carmustine, cyclophosphamide, melphalan, and prednisone.

Table 2. Number of Bortezomib Courses (B), State of the Disease, and Adverse Reactions (AR) or Complications

Patient	Number of Courses With B	State of the Disease[a]	AR/Complications
1	8	Partial response	Gastrointestinal disorder + neuropathy
2	7	Complete response	Neuropathy + neutropenia (grade II)
3	8	Partial response	Gastrointestinal disorder + neuropathy
4	2, 4, 8	Complete response	Acute tubular necrosis (grade III)
5	<2	?	Cholestasis + orthostatic hypotension
6	>4	?	–
7	8	Partial response	–
8	8	Complete response	Gastrointestinal disorder
9	<2	Death	–
10	<2	?	Neuropathy (grade III) + syncopal episodes
11	7	No response-death	–
12	6	Partial response	Severe gastrointestinal disorder

[a]State the disease after bortezomib treatment.
? indicates no data.

dexamethasone for the first course, and for the second, lenalidomide, bortezomib, and dexamethasone, with no response and death.

Of the 6 patients who did not complete the 7-8 courses of bortezomib, 4 were discontinued due to adverse effects or treatment complications, 1 died from myeloma progression (patient 9), and the other could not be evaluated because of continued treatment during the study period (patient 6). All cases were interrupted in the second course of bortezomib except for patient 12, who received 6 courses and reached partial response criteria.

Overall, adverse reactions or treatment complications were observed in 8 patients. The most frequent ones were gastrointestinal toxicity and neuropathy. Adverse reactions of patients with complete treatment were mild (grade I/II) and were resolved after a dose reduction to 1 mg/m^2 (Table 2).

For a patient with discontinued initial treatment of bortezomib because of renal insufficiency (patient 4), after 1 course of vincristine, doxorubicin, and dexamethasone, PAD was re-initiated with a reduced dosage of bortezomib (1 mg/m^2) and renal function monitoring, and after 4 courses, the patient showed a partial response. Subsequently, bortezomib combined with dexamethasone was re-initiated due to suspicion of disease progression, and partial response criteria were achieved after 8 courses of treatment. This patient continued on maintenance treatment with bortezomib every 15 days (3 doses) until an autologous transplant of haematopoietic progenitors was carried out. At 3 months post transplant, the patient showed complete remission of the disease and continued with maintenance treatment.

After the study period, a total of 8 patients survived, of which 6 had no progression. (Figures 1 and 2).

DISCUSSION

Bortezomib has shown efficacy in progressive MM treatment for patients who have received at least one previous treatment, and it shows better response that dexamethasone alone, based on results from various clinical trials.[12,13] In our study a response was obtained in 58% of patients treated with bortezomib (7/12), of which 25% (3/12) achieved complete response criteria, and 33% (4/12) partial response. These are better results than those obtained in various previous studies (degree of response 35%; partial response 18%; complete response 10%).[13] The good results obtained cannot be generalized because of: reduced sample size, not all patients were diagnosed with refractory MM, various dosage regimen, combinations of bortezomib used, and the number of treatment courses received.

Currently, even though thalidomide has more often been used as a rescue treatment for MM, it was only used on one of the patients of our study due to multiple administrative obstacles, both from the ministry and the laboratory. Our patient was in thalidomide treatment for 17 months, at a total cost of 47 420.8 €;

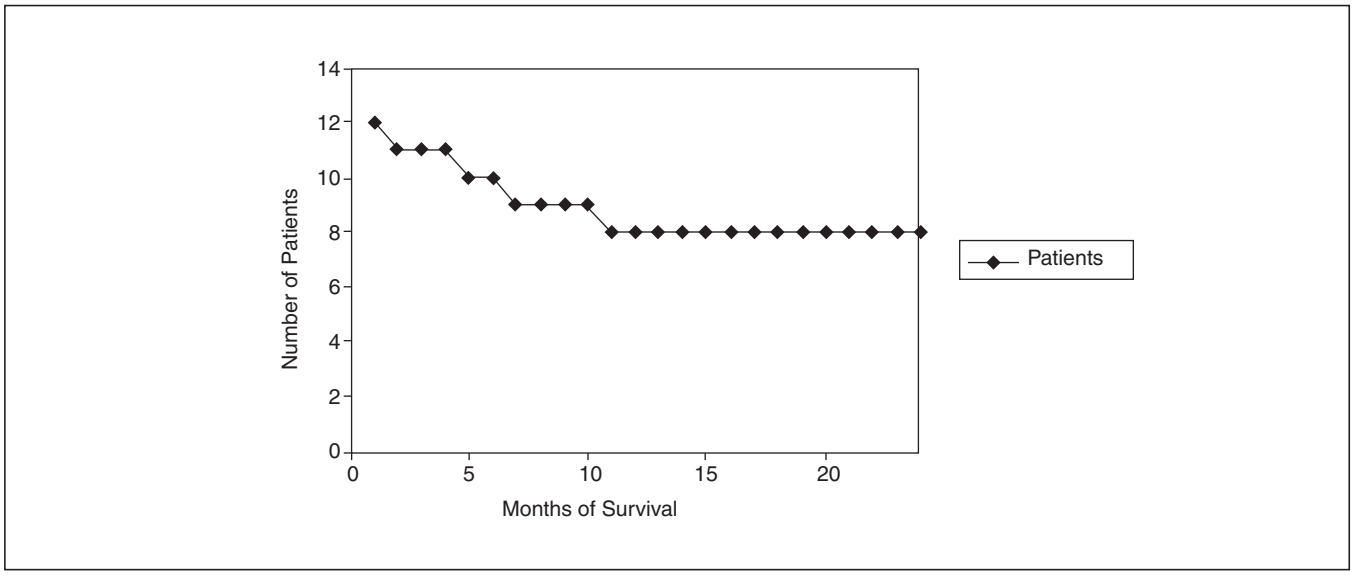

Figure 1. *Graph of overall survival of patients in bortezomib treatment.*

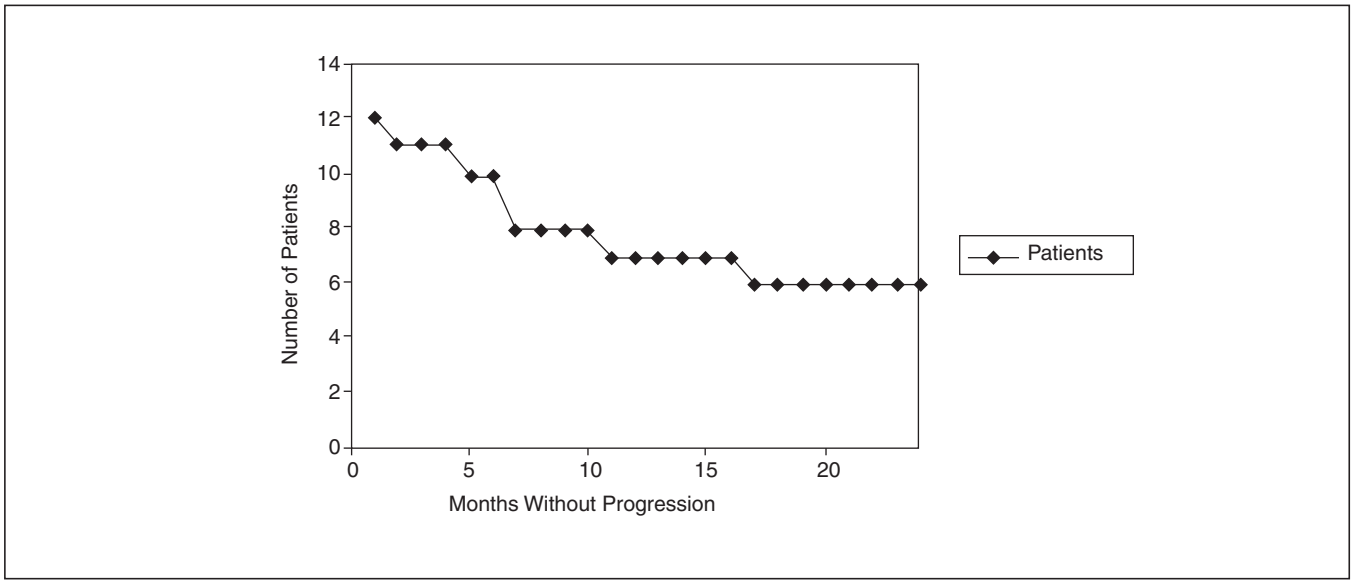

Figure 2. *Graph of overall survival with no progression of patients in bortezomib treatment.*

but the patient's bortezomib treatment (a total of 8 courses) was 17 920 €, and only 2 vials of bortezomib were used in each course due to its stability once opened (5 days).[4,14,15] Bortezomib has demonstrated efficacy as a first line treatment, by itself or in combination with other drugs, such as melphalan, prednisone, doxorubicin, dexamethasone, lenalidomide, or thalidomide, both in transplant candidates and non-candidates.[16-20] In our case, bortezomib was only used as a first line of treatment in 2 patients; one was diagnosed with plasma cell leukaemia and the other with solitary plasmocytoma.

Plasma cell leukaemia (before or after MM onset) is characterized by aggressive clinical development and is usually resistant to conventional chemotherapy,[21,22] and this is why bortezomib has been used on some patients with this type of leukaemia because of its demonstrated efficacy.[7,23,24] The patient diagnosed with plasma cell leukaemia in our hospital achieved complete response criteria after various therapeutic strategies with bortezomib and an autologous transplant of haematopoietic progenitors. This confirmed the drug's efficacy in treating this type of aggressive multiple-myeloma leukaemia.

Standard treatment for plasmocytoma, a single tumour of myelomatous cells with osseous or extraosseous localization, is radiotherapy or surgery.[2] This treatment is often problematic. Therefore, other treatment alternatives have been tested; among these is bortezomib with tumour resolution being observed after various courses.[6,25-27] In our study, 2 of the patients with osseous plasmacytomas associated with MM achieved complete response to bortezomib treatment and complete disappearance of plasmocytomas. The good results suggest that this drug should be considered an alternative for patients with plasmacytoma who do not respond to standard treatment or for those who cannot receive it.

The most frequent adverse reactions associated with bortezomib treatment in our study were gastrointestinal toxicity (50%) and neuropathy (50%), which coincide with those most commonly described in the bibliography.[4,12] Renal toxicity of one of our patients cannot be tied to bortezomib treatment safety, because there were other accompanying circumstances (treatment with aminoglycoside antibiotics, infectious symptoms, and hypovolaemia) which may also induce kidney failure. In fact, there are cases of patients with renal insufficiency who have tolerated a complete dosage of bortezomib, and achieved response and even improvement of renal failure.[28] This is why continued bortezomib therapy was chosen for this patient. In a few studies, neuropathy has shown to be more frequent if patients with malignant gammopathy present with underlying neuropathy or diabetes mellitus.[29] In our case, the neuropathy appeared with treatment and no data were collected on whether patients presented with diabetes mellitus. After the appearance of toxicity with treatment, recommended dosage adjustments were made.[4] Some patients did not return to treatment, due to grade III-IV toxicity or the patient's request.

In conclusion, bortezomib has shown good results in malignant gammopathy treatment, and in our case, especially in treatment of plasmocytoma and plasma cell leukaemia. The use of new drugs such as bortezomib in treating these neoplasias improves response and survival of patients, but more studies and better knowledge of the biology of these diseases are still needed.

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