

Three Cases of Bortezomib-resistant Multiple Myeloma with Extramedullary Masses

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In some patients with multiple myeloma, extramedullary masses may be present at diagnosis or may develop during treatment. Recently, multiple myeloma has been treated using newer therapeutic regimens based on thalidomide and bortezomib. Using these drugs, positive responses to treatment, not found with conventional antineoplastic agents, have been reported along with an improvement in patient outcome. In the present study, we report on three patients with extramedullary masses associated with multiple myeloma. Although all three patients were treated with bortezomib, it was ineffective against the extramedullary masses and the clinical course of the disease differed between the three patients. We propose that the effects of bortezomib on extramedullary masses may differ from case to case and may not be evident in cases of severe disease. Also, the effects of bortezomib may not be evident in the case of myeloma cells that have left the bone marrow microenvironment, similar to thalidomide. In addition, resistance to bortezomib may manifest as extramedullary masses. (160 words in the body of abstract)

Key words: bortezomib, extramedullary mass, plasmacytoma, multiple myeloma, treatment

INTRODUCTION

Multiple myeloma (MM) is a systemic malignancy of plasma cells. This disease is clinically characterized by bone pain with lytic bone lesions and/or severe osteopenia, anemia, hypercalcemia, renal function impairment, recurrent infections and the presence of extramedullary involvement. The development of soft-tissue plasmacytomas has been reported in 15-20% of the patients at the time of diagnosis and in an additional 15% during the course of the disease [1-2]. Recently, several novel agents have been introduced for the treatment of MM [3-9]. Bortezomib, thalidomide and lenalidomide target both plasma cells and the bone marrow microenvironment.

Bortezomib is a potent and selective proteasome inhibitor. This drug produced significant responses with advanced progressive refractory and relapsed MM, including extramedullary masses [4-7]. In the present study, we report three cases of relapsed MM with extramedullary mass which were resistant to bortezomib therapy.

CASE REPORTS

From August 2004 to August 2008, 17 consecutive patients with relapsed or refractory MM (11 male/6 female) were treated with bortezomib therapy in our institute. Four patients had refractory MM while 13 patients had relapsed MM. Three out of 17 patients had extramedullary plasmacytomas when treatment with bortezomib was initiated. The clinical course of each

of these three patients is briefly detailed in this report.

Case 1: A 48-year-old woman was diagnosed with stage III MM using the International Scoring System (ISS) criteria [10]. Cytogenetic abnormalities involving the deletion of 13 were detected with conventional karyotyping. She achieved a complete response after 2 cycles of VAD (vincristine, doxorubicin and dexamethasone) therapy (Fig. 1A). She was then given high-dose cyclophosphamide therapy prior to the collection of her hematopoietic stem cells for high-dose chemotherapy. However, an insufficient quantity of stem cells was harvested. She relapsed with multiple liver plasmacytomas one month later (Fig. 1B). She showed clinical and serological disease progression while on one cycle of bortezomib (1.3 mg/m²) therapy and finally died 6 months later from the diagnosis. An autopsy revealed multiple organ failure due to myeloma cell invasion. Autopsy specimens as well as an initial bone marrow biopsy specimen revealed a massive proliferation of plasmablastic myeloma cells.

Case 2: A 54-year-old man was diagnosed with stage III MM with a thoracic vertebral plasmacytoma. Bone marrow cells showed the normal karyotype with conventional karyotyping. He was given local radiation therapy (40 Gy) prior to 2 cycles of VAD therapy, and subsequently given 8 cycles of MP (melphalan plus prednisolone) therapy achieving a partial response. The disease progressed eight months later and bortezo-

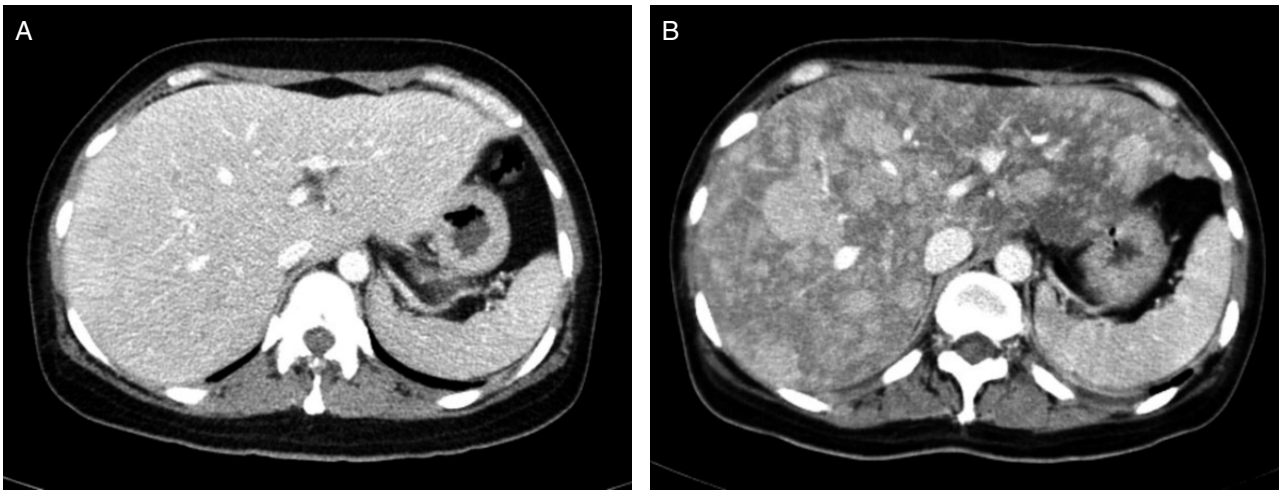


Fig. 1 CT scan showed clear multiple masses in liver (B) which were not present at admission (A) (case1).

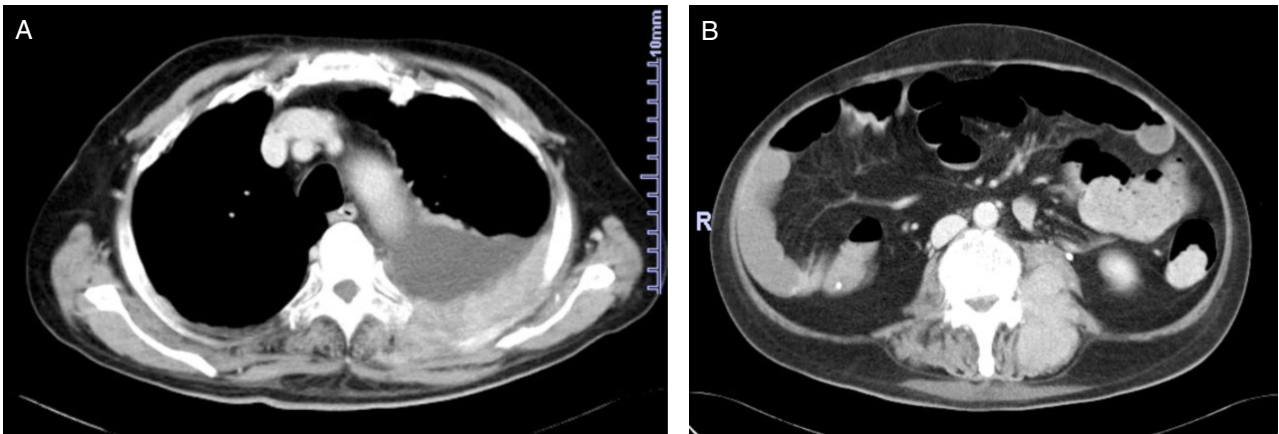


Fig. 2 A massive pleural effusion was observed in the left side. A large mass along the rib in the left thoracic wall (A) and in the pelvis (B) appeared during radiotherapy (case2).

mib (1.3 mg/m^2) was initiated. In spite of the initial response with the serum monoclonal protein (M protein), he developed extramedullary masses at the third to sixth thoracic vertebrae (Th3-6) and the first lumbar vertebrae (L1) after 3 cycles of bortezomib therapy. He was given local radiation therapy (25 Gy and 30 Gy, Th3-6 and L1, respectively). While on radiation therapy, a massive pleural effusion in the left chest, a large extramedullary mass along the rib in the left thoracic wall and an extramedullary mass in the pelvis appeared (Fig. 2AB). Combination chemotherapy with multiple agents (melphalan, cyclophosphamide, doxorubicin and vincristine) was not effective and he died eventually 2 years and 8 months later. Although the extramedullary masses in this patient grew rapidly, M protein level continued to decrease until just before his death. Autopsy findings showed that myeloma cells had invaded multiple organs. An initial bone marrow biopsy revealed a diffuse proliferation of mature myeloma cells. Also, a massive proliferation of plasmablastic myeloma cells was found in autopsy specimens.

Case 3: A 58-year-old man was diagnosed with stage I MM. Bone marrow cells showed the normal karyotype with conventional karyotyping. He was

monitored without treatment since he presented with no symptoms. Two years later after the initial diagnosis, he progressed into stage II with increasing serum M-protein. He was given 4 cycles of VAD therapy achieving a complete response. He was given high-dose cyclophosphamide therapy for the collection of hematopoietic stem cells. However, an insufficient quantity of stem cells was harvested. He relapsed 8 months later with increasing serum M-protein. With bortezomib treatment (1.3 mg/m^2), he showed a rapid M-protein response. However, the treatment was impossible after 4 cycles because a severe edema and eruption developed. Serum M-protein increased 4 months later and he was given a salvage treatment with bortezomib at a reduced dose of 1.0 mg/m^2 . Although he showed a partial response until cycle 3 of bortezomib therapy, he developed extramedullary masses in his right thoracic wall (Fig. 3A). The lesions decreased after 20 Gy of local radiation, but a massive right pleural effusion and a new extramedullary mass projecting into the thoracic cavity developed (Fig. 3B). He died due to acute respiratory failure. Although the extramedullary masses in this patient grew rapidly, the M protein response continued until just before his death. An autopsy was not performed.

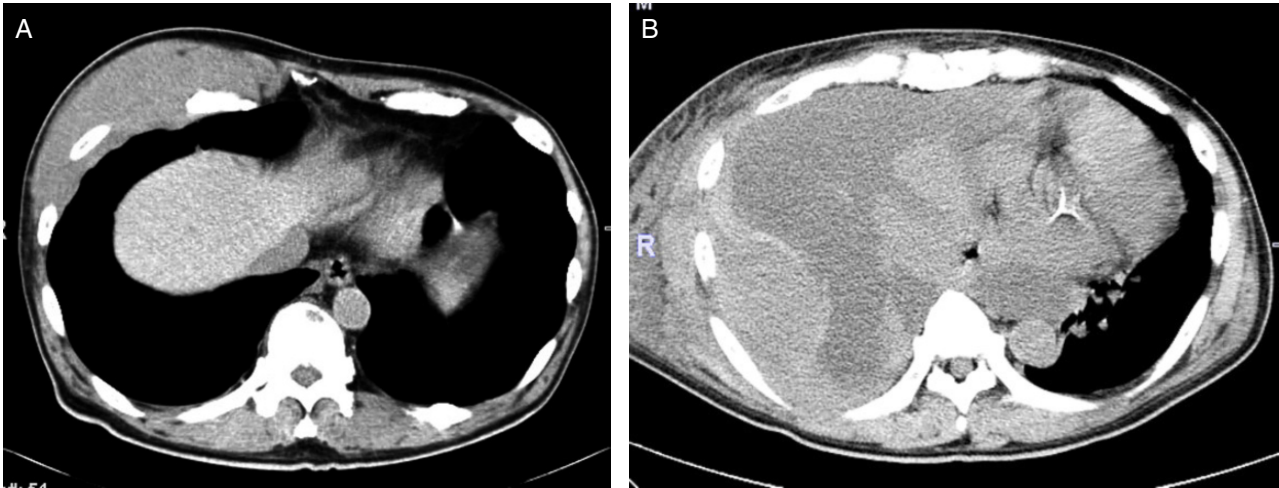


Fig. 3 An extramedullary mass appeared on the right thoracic wall (A). A massive right pleural effusion and a new mass, which projected into the thoracic cavity, developed during the treatment (B) (case3).

DISCUSSION

Following recent developments in molecular target therapy, an increased frequency of extramedullary masses in hematopoietic malignancy has been noted [3]. It is believed that this is partly due to improved survival which allows for exacerbation of the condition by normally dormant cells. In addition, the use of new drugs in the treatment of multiple myeloma, with different mechanisms of action from conventional antineoplastic drugs, may have contributed to the increased frequency of extramedullary masses.

Bortezomib is an active anti-myeloma agent which produces responses in about one-third of patients with heavily pretreated resistant disease. The mechanism of action of bortezomib is thought to be partly due to the selective inhibition of proteasomes. This drug has been reported to affect myeloma cell growth either by NF- κ B blockade, the down-regulation of adhesion molecules, inhibition of angiogenesis and/or by inhibiting DNA repair, all of which results in a proapoptotic effect on MM [11]. There are many reports of bortezomib being effective in the treatment of extramedullary masses due to the direct effect of bortezomib on myeloma cells [4-7]. However, Ali *et al.* have reported a case in which bortezomib was not effective in the treatment of an extramedullary disease in MM [8]. In this case, the patient was diagnosed with stage II MM and had an extramedullary mass. The patient relapsed with only the extramedullary disease, and had no bone marrow involvement after a complete remission had been achieved with MP therapy. In this instance, bortezomib was not effective at all after the third course of treatment.

In the present study, we report on three cases in which extramedullary masses developed during treatment for MM. The clinical course of the disease in each patient was different and bortezomib failed to exhibit any efficacy against the extramedullary masses, although serum M protein was controlled in case 2

and 3. Terpos *et al.* described that all 15 patients with extramedullary mass among 147 patients with MM relapsed in the absence of systemic progression post-high-dose therapy for MM. Extramedullary relapse occurred prior to medullary relapse, suggesting the presence of an extramedullary clone of plasma cells with a high degree of chemo-resistance [12].

In the first case, bortezomib had no effect on the rapidly growing extramedullary mass; in the second case, the extramedullary masses developed regardless of decreases in M protein level during the course of treatment; and in the third case, the extramedullary masses developed at the final stages after a long period of treatment with bortezomib. Subsequently, all patients died as a result of a rapid exacerbation of the MM. All our cases showed different clinical courses in each or previous reports. Alegre *et al.* has described that the patterns of relapse of MM after high-dose therapy are very heterogeneous [13]. These different expressions of relapse may be due to clonal selection after high-dose therapy and could indicate the persistence of a resistant clone after intensification therapy. In the same way, the different clinical courses of our patients may be due to clonal selection after bortezomib therapy.

It has been reported that disseminated extramedullary masses develop in the acute phase of treatment for multiple myeloma [14]. It may be reasonable not to expect bortezomib to exhibit a great deal of efficacy in these patients because their condition is too poor. However, it is interesting that a systemic relapse did not develop, despite progression of the extramedullary masses. MM may show extramedullary progression independently from the medullary disease. We suggest that the response to bortezomib may differ between cases, although bortezomib may not be an effective agent for extramedullary masses in MM. The progression of myeloma cell homing in different tissues may affect the response to therapy, and it may become tolerant to bortezomib.

Table 1 Characteristics of patients with or without extramedullary masses at bortezomib initiation

patient	age/sex	M-protein type (mg/dl)	stage	BMPC (%)	B2MG (mg/dl)	LDH (u/l)	extramedullary masses
1	48/F	IgG/3328	IIIA	94.2	10.66	787	liver
2	54/M	IgA/7670	IIIA	25.2	10.28	279	-
3	58/M	IgG/5300	IIA	21.0	4.73	246	-

BMPC, bone marrow plasma cells; B2MG, beta-2-microglobulin; LDH, lactate dehydrogenase, normal value < 300 u/l; Ig, immunoglobulin.

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