

Complete Response Obtained by Bortezomib plus Dexamethasone in a Patient with Relapsed Multiple Myeloma with Multiple Plasmacytomas

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Abstract. *Background:* A case of relapsed multiple myeloma (MM) with multiple plasmacytomas of the parietal bone and the right orbit in which was achieved a complete response with bortezomib plus dexamethasone (BD) therapy is reported. A Japanese woman with Bench-Jones lambda-type MM who achieved a plateau phase with nine courses of melphalan plus prednisolone therapy complained of right exophthalmos and numbness around her mouth. Computed tomographic (CT) scan and T2-weighted magnetic resonance imaging showed tumours at the parietal bone and the right orbit. A tumour biopsy from the parietal bone revealed the histological morphology of a plasmacytoma. She was therefore diagnosed with relapsed MM with multiple plasmacytomas, and received BD therapy. A CT scan after the end of the second course of treatment revealed the disappearance of the plasmacytomas. At the end of the fifth course, no lambda light chain was detected by immunofixation of serum and urine, and the pathological plasma cells in bone marrow were fewer than 5%; therefore, she had achieved a complete response. The time to disease progression from the first course of BD therapy and the treatment-free interval were 400 days and 134 days, respectively. *Conclusion:* This case report indicates that bortezomib may be a promising agent for MM with multiple plasmacytomas.

Multiple myeloma (MM) is a haematological malignancy characterized by monoclonal proliferation of plasma cells and the presence of monoclonal immunoglobulin in serum and

urine. Its common clinical features are anaemia, renal dysfunction, osteolysis and hypercalcaemia (1, 2). In the past decade, there have been major advances as a result of new anti-myeloma agents (3). A proteasome inhibitor, bortezomib, is one of these new agents (4, 5) and has been successfully used for the treatment of MM (6-8).

However, the development of plasmacytomas has been seen at the time of diagnosis or during the course of MM (9). Although the development of plasmacytomas is considered to be associated with aggressive disease and a poor prognosis of MM (10), a treatment strategy for MM with multiple plasmacytomas has not been established.

Recent reports have mentioned the efficacy of bortezomib for extramedullary plasmacytomas or MM with plasmacytomas (11-20). In this case study, a patient is reported with relapsed MM with multiple plasmacytomas of the parietal bone and the right orbit who achieved a complete response with bortezomib plus dexamethasone (BD) therapy.

Case Report

A previously healthy 68-year-old Japanese woman was referred to the host hospital with lumbago in July 2007. A radiographic bone survey revealed multiple osteolytic lesions in the skull, spines, ribs, humerus, thighbones and pelvic bones. Her peripheral blood analysis showed anaemia (haemoglobin 9.3 g/dl), but the white blood cell and platelet counts were normal. The bone marrow was normocellular and contained 22% pathological plasma cells, which were positive for CD138, CD79 α and cytoplasmic lambda light chain, and negative for CD20 and T-cell markers. Lambda light chain was detected by immunofixation of serum and urine. Serum albumin and β 2-microglobulin were 44 g/l and 6.6 μ g/ml, respectively; therefore, she was diagnosed with Bench-Jones lambda-type MM (stage 3 and stage III-A according to the International Staging System, and Durie and Salmon Staging System, respectively). At the time of initial diagnosis, no plasmacytomas were detected by a whole-body computed

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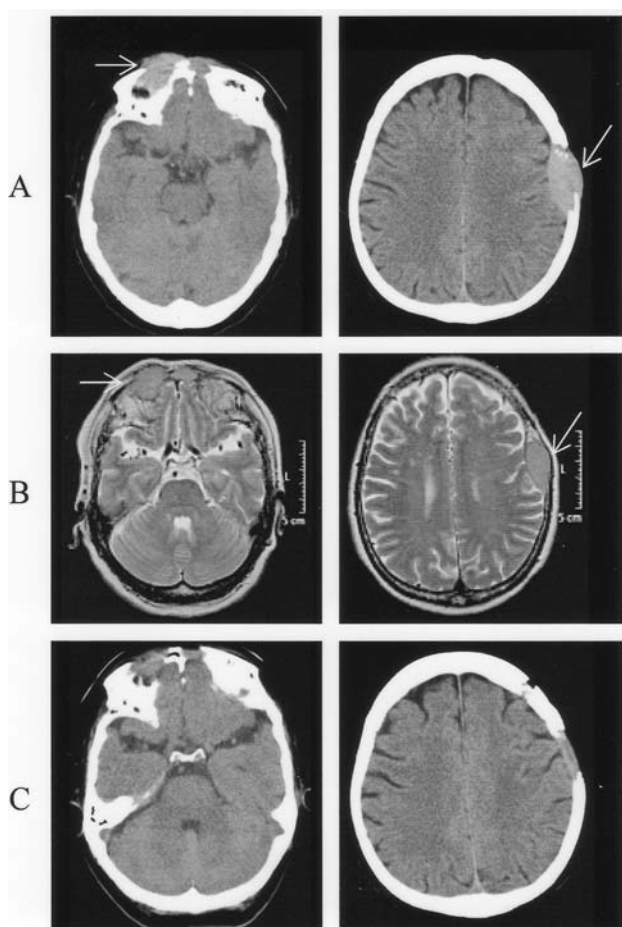


Figure 1. Computed tomographic (CT) scan and magnetic resonance imaging (MRI) before and after bortezomib plus dexamethasone (BD) therapy. A: CT scan before BD therapy. B: MRI before BD therapy. Arrows indicate plasmacytomas at the parietal bone and right orbit. C: CT scan at the end of the second course of BD therapy. Plasmacytomas disappeared despite osteolytic lesions.

tomographic (CT) scan. She achieved a plateau phase with nine courses of melphalan plus prednisolone (MP) therapy. Two months after the last MP therapy, she complained of right exophthalmos and numbness around her mouth. CT scan and T2-weighted magnetic resonance imaging (MRI) showed tumours at the parietal bone (size: 40×20 mm) and the right orbit (size: 30×25 mm) (Figure 1A, B). A tumour biopsy from the parietal bone revealed the histological morphology of a plasmacytoma (Figure 2). The bone marrow was normocellular and contained 23% pathological plasma cells. Bone marrow cell karyotyping revealed multi-complex abnormalities, including chromosome 13 deletion in metaphases which had not been detected at the diagnosis of MM in 2007. She was diagnosed with relapsed MM with multiple plasmacytomas. BD therapy was chosen to achieve rapid control of MM, especially plasmacytomas. Bortezomib at 1.3 mg/m² was

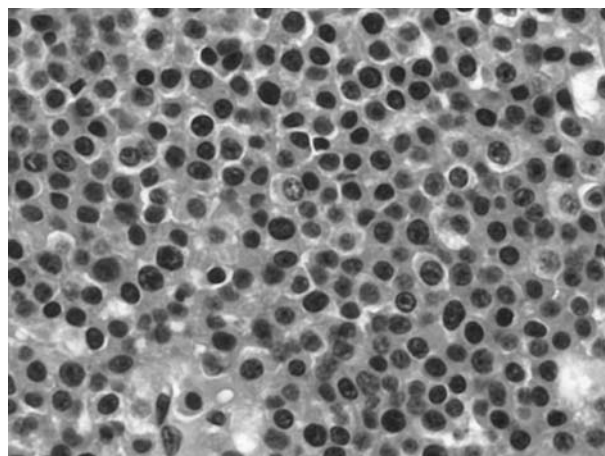


Figure 2. Tumour biopsy from the parietal bone. The diffuse infiltration of plasma cells was compatible with the histological morphology of a plasmacytoma.

administered intravenously at days 1, 4, 8 and 11 of each 21-day cycle during the first and second courses. Dexamethasone (10 mg/body/day) was given orally on the day of and day after bortezomib treatment. During the first course of BD therapy, the right exophthalmos and numbness around her mouth disappeared completely. A CT scan at the end of the second course of BD therapy revealed the disappearance of the plasmacytomas despite osteolytic lesions (Figure 1C). Subsequently, 1.3 mg/m² bortezomib was administered at day 1, 8, 15 and 22 of each 35-day cycle during the third and seventh courses of BD therapy. At the end of the fifth course, no lambda light chain was detected by immunofixation of serum and urine, and the pathological plasma cells in bone marrow were fewer than 5%; therefore, she had achieved a complete response according to the criteria of the International Myeloma Working Group (21) and BD therapy was ended after the seventh course.

The most severe adverse event assessed by the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 was thrombocytopenia (grade 3 during the first and second courses and grade 1 during the third and seventh courses) which recovered by the next course. Four months after the last BD therapy, her MM clinically relapsed again associated with plasmacytoma of the vertebral canal. The time to disease progression from the first course of BD therapy and the treatment-free interval were 400 days and 134 days, respectively.

Discussion

Extramedullary involvement has been reported in one-third of patients at diagnosis or during the course of MM (9). Although the development of plasmacytomas is considered

to be associated with aggressive disease and a poor prognosis of MM (10), a treatment strategy for MM with multiple plasmacytomas has not been established.

Because plasmacytomas have elevated angiogenic activity (22), anti-angiogenic agents may be effective. Thalidomide has been considered an anti-angiogenic agent (23) and is effective for MM (24, 25): However, there are some reports that thalidomide is not effective for plasmacytomas (10, 26, 27); some patients showed progression of the plasmacytomas despite a good serological response (26, 27). The reasons for the different response to thalidomide of bone marrow and plasmacytomas are unknown, but the anti-angiogenic activity of thalidomide might be insufficient to inhibit the growth of plasmacytomas. Indeed, in *in vivo* models, the inhibitory effect of thalidomide on angiogenesis was lower than that of lenalidomide (28).

Bortezomib is a proteasome inhibitor with significant activity in MM (4, 5), and its clinical efficacy has been established in previous studies (6-8). Thalidomide is effective in patients with relatively indolent disease while bortezomib is also effective in patients with more aggressive myeloma. It was reported that bortezomib appears to overcome the poor prognosis of chromosome 13 deletion (29). Furthermore, some reports have mentioned the efficacy of bortezomib for extramedullary plasmacytomas or MM with plasmacytomas (11-20). In this patient, despite chromosome 13 deletion, plasmacytomas disappeared quickly, and a complete response was obtained by BD therapy. Roccaro *et al.* reported that bortezomib inhibited the proliferation of multiple myeloma patient-derived endothelial cells and human umbilical vein endothelial cells in a dose- and time-dependent manner, and down-regulated vascular endothelial growth factor, interleukin-6, insulin-like growth factor-I, angiopoietin 1 (Ang1), and Ang2 transcription (30). These anti-angiogenic properties of bortezomib may contribute to its clinical efficacy for plasmacytomas.

In conclusion, this case report indicates that bortezomib may be a promising agent for extramedullary plasmacytomas or MM with multiple plasmacytomas. Prospective trials should be conducted to confirm the efficacy of bortezomib for extramedullary plasmacytomas or MM with plasmacytomas.

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