CASE REPORT

Refractory Plasmablastic Type Myeloma with Multiple Extramedullary Plasmacytomas and Massive Myelomatous Effusion: Remarkable Response with a Combination of Thalidomide and Dexamethasone

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Abstract

A 74-year-old man with multiple myeloma was refractory to melphalan/prednisolone (MP), high-dose dexamethasone and VAD chemotherapy. He had the following poor prognostic factors: 1) multiple extramedullary plasmacytomas, 2) massive myelomatous effusion, 3) increasing immature myeloma cells with plasmablastic morphology, and 4) predominance of MPC1-CD49e-CD45+ phenotype immature myeloma cells. Combination therapy with thalidomide and dexamethasone resulted in a rapid response and a partial remission despite his multiple poor prognostic factors. The present case suggests that combination therapy with thalidomide and dexamethasone is still an alternative treatment regimen for resistant extramedullary plasmacytoma with a plasmablastic morphology.

Key words: multiple myeloma, extramedullary plasmacytoma, thalidomide

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Introduction

Multiple myeloma (MM) is a plasma cell malignancy that remains fatal despite the use of high dose chemotherapy with hematopoietic stem cell transplantation (1). Thalidomide has been demonstrated to be effective for refractory MM (2). In addition, the combination of melphalan and prednisolone with thalidomide (MPT) is also an effective first-line treatment for elderly patients with multiple myeloma (3). Extramedullary plasmacytomas have been reported in 15-20% of patients at diagnosis and in an additional 15% during the course of multiple myeloma (4, 5). These patients usually have a poor prognosis even with aggressive treatment. The efficacy of thalidomide in patients with extramedullary plasmacytoma appears less encouraging. Here, we present a refractory multiple myeloma patient with multiple extramedullary plasmacytomas and massive myelomatous pleural effusion who showed a good response to combination therapy with thalidomide and dexamethasone.

Case Report

A 74-year-old man was diagnosed to have multiple myeloma (IgGκ, Durie-Salmon stage IA, ISS stage I) in April 2004. The myeloma cells at diagnosis showed a mature morphology and a chromosome analysis revealed a normal karyotype. Because he was asymptomatic with no organ or tissue impairment, he was initially observed closely without any treatment. Two years later, his serum IgG level had increased to 7,085 mg/dL, while his hemoglobin level fell to 8 g/dL. Multiple bone fractures of his ribs and spine also occurred. A diagnosis of symptomatic myeloma, Durie-Salmon stage IIIA, was made on the basis of these findings and a monthly regimen of melphalan and prednisolone (MP) was thus administered. He maintained partial response (PR) following 12 courses of MP. But one year later, he showed a progressive rise in IgG with a drop in hemoglobin. A laboratory evaluation revealed a serum IgG level of 6,000 mg/dL, hemoglobin of 6 g/dL, while the IgA and IgM levels were low. Serum LDH was 287 IU/L, Beta2-
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Figure 1. A flow cytometry analysis with the CD38 plasma gating method. A, MPC1 – CD49e – CD45+ phenotype immature myeloma cells were predominant in the BM. B, Morphological findings with May-Giemsa staining confirmed the characteristics of immature large myeloma cells with a plasmablastic morphology in the pleural fluid. C, MPC1 – CD49e – CD45+ phenotype immature myeloma cells were also predominant in the pleural fluid.

Microglobulin was 6.2 mg/dL and CRP was 0.4 mg/dL. He was treated with one course of high dose dexamethasone and one course of vincristine/doxorubicin/dexamethasone (VAD) but there was no response to these therapies. Bone marrow (BM) aspirate showed 20% of immature plasma cells of 20% with plasmablastic morphology. A flow cytometric analysis of BM myeloma cells using the CD38 plasma gating method showed a predominance of MPC1-CD49e-CD45+ phenotype immature myeloma cells (Fig. 1A). A karyotype analysis showed complex abnormalities (neither 13q- nor 17p- were detected). Peripheral blood smear showed 3% myeloma cells with plasmablastic morphology. The patient received several transfusions of red cells for anemia caused by the disease progression. A chest radiograph (Fig. 2) and CT scan revealed extramedullary plasmacytomas in the right chest wall and paravertebral space, and bilateral massive pleural effusions (Fig. 3A, B). Thoracentesis was thereafter performed and a cytospin preparation of the pleural fluid showed many immature large plasma cells with a plasmablastic morphology (Fig. 1B). A flow cytometric analysis of the pleural fluid revealed a predominance of MPC1-CD49e-CD45+ phenotype immature myeloma cells (Fig. 1C). A subcutaneous mass also appeared in the left abdominal wall. An upper gastrointestinal endoscopic evaluation demonstrated multiple gastric polyps, from which multiple biopsy specimens were obtained. A histological examination revealed gastric plasmacytoma (Fig. 3C).

His poor performance status contraindicated the use of bortezomib. He fell into respiratory failure due to the bilateral massive pleural effusion, and thus thalidomide monotherapy (100 mg daily) was initiated after informed consent was obtained. Although the daily thalidomide dose was increased to 200 mg, there was no response to thalidomide alone. High-dose dexamethasone (40 mg/day) was administered for four days and then continued combination treatment with thalidomide and low-dose dexamethasone (4 mg/day) was given. A dramatic clinical improvement was thereafter achieved within one month (Fig. 2). The patient’s condition improved gradually and he did not need transfusions after the treatment, and the proportion of myeloma cells in the BM decreased from 20% to 1.5% after one month. Myeloma cells in the peripheral blood smear became undetectable. Serum IgG level also decreased from 5,221 mg/dL to 1,119 mg/dL. A chest radiograph (Fig. 2) and CT scan showed a marked reduction in the size of the extramedullary plasmacytomas in the right chest wall, and paravertebral space (Fig. 3D, E). The bilateral massive pleural effusion also dramatically improved. Subsequent endoscopy showed only signs of healing scars and gastric biopsies revealed no evidence of plasmacytoma (Fig. 3F). Despite a good response to thalidomide and low-dose dexamethasone, it was necessary to decrease the dose of thalidomide to 100 mg/day three months after the start of thalidomide treatment because of peripheral neuropathy. However, the plasmacytoma in the right chest wall gradually increased in size. The dose of thalidomide was then again increased to 200 mg, but new subcutaneous tumors occurred in the right forearm and the left chest wall. High-dose dexamethasone (40 mg/day, four
days) was administered and the plasmacytomas gradually reduced again. However, it was necessary to discontinue thalidomide treatment because of severe peripheral neuropathy. After the cessation of thalidomide, multiple extramedullary plasmacytomas occurred throughout the patient’s entire body. He died due to septic complications 8 months after the start of the combination therapy with thalidomide and dexamethasone.

**Discussion**

Multiple myeloma (MM) is a plasma cell malignancy that remains fatal despite the use of high dose chemotherapy with hematopoietic stem cell transplantation. Therefore, a new potent therapeutic strategy is needed for the treatment of refractory MM patients.

This report presents a case of a refractory plasmablastic type myeloma with multiple extramedullary plasmacytomas and massive myelomatous effusion. This patient had the following poor prognostic factors: 1) multiple extramedullary plasmacytomas including gastrointestinal (GI) involvement, 2) massive myelomatous effusion, 3) plasmablastic morphology, and 4) MPC1-CD49e-CD45+ immature phenotype.

Extramedullary involvement by MM has been reported in 15%-20% of patients at the time of diagnosis and in an additional 15% during the course of the disease (4, 5). Extramedullary plasmacytomas have been observed in lymph nodes, skin, liver, GI tract, kidney and meninges in the course of MM. These patients usually have a poor prognosis even with aggressive treatment approaches. The involvement of the GI tract in the course of MM is extremely rare (6). Grogen and Spier reported that GI involvement by MM is rare, representing less than 5% of all extramedullary plasmacytoma (7). The prognosis of MM patients with GI involvement is very poor, even after aggressive treatment.

Pleural effusion in multiple myeloma is relatively infrequent and myelomatous pleural effusion is extremely rare. Kintzer et al analyzed 958 cases of multiple myeloma, 58 patients with pleural effusion and pleural involvement in 8 cases (8). Multiple myeloma associated with myelomatous effusion has a very poor prognosis with a reported length of survival of less than four months (9). The effusion is thought to be a late manifestation in the natural history of multiple myeloma or an expression of the aggressive behavior of the disease.

In the present case, immature myeloma cells with plasmablastic morphology were increased in both the BM and pleural fluid. Twenty years ago, Greipp et al classified myeloma cells as mature, intermediate, immature, and plasmablastic, and they showed that plasmablastic morphology is an independent predictor of poor survival after autologous stem cell transplantation (10, 11). On the other hand,

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**Figure 2.** Clinical course of the patient. HDD indicates high dose dexamethasone; VAD indicates vincristine, doxorubicin, and dexamethasone; BM: bone marrow, PN: peripheral neuropathy.
Kawano et al classified myeloma cells according to phenotype into the following 3 types: immature (MPC1-CD49e-CD45+/−), intermediate (MPC1+CD49e-CD45−), and mature (MPC1+CD49e+/−CD45+) (12, 13). The phenotype-based classification shows a good correlation with that based on morphology. These authors also demonstrated that only a few subpopulations of tumor cells, such as MPC1-CD49e-CD45+ immature myeloma cells, proliferate in response to interleukin 6 (14). MPC1-immature myeloma cells increase significantly to greater than 25% of myeloma cell fractions in the progressive states of MM. MPC1- myeloma cells have been reported to show immature or blastic morphology and higher uptakes of tritiated thymidine in in vitro culture (15). The expression of CD45 is also considered to be critical for the IL-6-induced proliferation of these MPC1-immature myeloma cells. MPC1-CD45+ immature cells are able to respond to IL-6 to proliferate in vitro and are considered proliferative fractions in the BM of MM patients.

In the current case, one cycle of high-dose dexamethasone (40 mg/day, 4 days)/thalidomide (200 mg/day) was administered followed by continuous low dose dexamethasone (4 mg/day) and thalidomide (200 mg/day) as maintenance therapy, which was well tolerated without severe hematologic toxicities. Although it was necessary to decrease the dose of thalidomide three months after the start of thalidomide treatment due to peripheral neuropathy, this therapy induced a very good response with a good quality of life during the three-month treatment period. Okikawa et al suggested that immature myeloma cells may be resistant to thalidomide (16). Since the effect of thalidomide on patients with refractory MM has been confirmed, its effect might be best on mature myeloma cells. Although thalidomide alone and in combination has demonstrated effectiveness in both a fall in monoclonal paraprotein levels and marrow plasmacytosis, the activity in patients with extramedullary plasmacytoma appears less encouraging. It is hypothesized that there could be differences in the microvascular supply of marrow and extramedullary plasmacytomas accounting for the difference in response. Blade et al described a lack of response in the extramedullary plasmacytomas of 5 patients despite reduction of the paraprotein in 3 patients (4). Myers et al reported a lack of response in the extraosseous disease of 2 patients treated with thalidomide despite a reduction in monoclonal paraprotein (17). Rosinol et al also reported that although four of the 11 MM patients with extramedullary involvement had a serological response to thalidomide, a progression of the soft-tissue masses was nevertheless observed in all of them (5). On the other hand, Biagi et al reported three patients who underwent autologous bone marrow transplantation and subsequently relapsed with extramedullary disease, which all responded to thalidomide (18). These authors postulated that the efficacy of thalidomide on extramedullary involvement after transplant could therefore be different than that observed in patients who receive only conventional chemotherapy. Similarly, Terpos et al reported the successful use of thalidomide in three patients with extramedullary relapse post-autologous stem cell transplantation (19). Combination therapy with thalidomide and dexamethasone increases the response rate, even in patients previously resistant to both drugs given as single agents, thus indicating the possibility of a synergistic effect. Weber et al reported results of a trial of thalidomide in combination with intermittent pulse dexamethasone (20). In 47 patients with resistant myeloma, 22 patients (46%) were resistant to both thalidomide and pulse dexamethasone given separately as single agents. The possibility of synergy between thalidomide and dexamethasone was supported by the surprising response rate of 46% in patients resistant to both drugs given previ-
ously as single agents. This result was similar to the overall response rate of 52%. Though there is strong data for the efficacy of newer agents such as thalidomide and bortezomib in the management of patients with myeloma, evidence for their use in extramedullary plasmacytoma is based on case reports only. Some authors reported that thalidomide in combination with dexamethasone and chemotherapy is more effective than thalidomide alone for extramedullary plasmacytoma. Gonzalez-Porras et al reported that thalidomide in combination with cyclophosphamide and dexamethasone (thac dex) was effective in soft-tissue plasmacytomas (21). Katodritou et al also reported the efficacy of the combination therapy with thalidomide and dexamethasone for the extramedullary plasmacytoma of the cavernous sinus (22). Dytfeld et al reported that bortezomib in combination with thalidomide and dexamethasone was effective for refractory extramedullary plasmacytoma of the cavernous sinus (23). Katodritou et al also reported the efficacy of the combination therapy with thalidomide and dexamethasone for the extramedullary plasmacytoma of the cavernous sinus (22). Dytfeld et al reported that bortezomib in combination with thalidomide and dexamethasone was effective for refractory plasmacytoma in the intravertebral space (23). In the current case, the possibility of a synergistic effect between thalidomide and dexamethasone was supported by the rapid response despite the resistance to both drugs given previously as single agents.

We administered low-dose dexamethasone with thalidomide continuously as maintenance therapy in this case. Mye rs et al reported the efficacy of the combination of continuous low-dose dexamethasone and thalidomide for advanced myeloma patients (24). Murakami et al reported the results of a non-randomized phase II study of low-dose thalidomide plus low-dose dexamethasone therapy in 66 patients with refractory multiple myeloma (25). The overall response rate was 63.6%, and progression-free and overall survival periods were 6.2 and 25.4 months. Relatively few adverse events were noted. These findings suggest that low-dose thalidomide plus low-dose dexamethasone therapy is as effective as high-dose thalidomide plus high-dose dexamethasone therapy in patients with refractory multiple myeloma. Low-dose dexamethasone with thalidomide may be a suitable treatment regimen for elderly patients with a poor performance status like our case.

In summary, the present case suggests that the combination therapy with thalidomide and dexamethasone may be an effective treatment regimen for resistant extramedullary plasmacytoma with immature plasmablastic morphology, and its efficacy should therefore be determined in a larger series.

References

