Successful Treatment of Immunoglobulin D Myeloma by Bortezomib and Dexamethasone Therapy

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Abstract

Immunoglobulin D (IgD) myeloma is a rare subtype and it is widely accepted as an aggressive disease. Here, we report a 66-year-old woman with IgD myeloma who had anemia, lumbago, multiple osteolytic lesions and hypercalcemia. The patient refused a blood transfusion because of her beliefs, so we administered bortezomib and dexamethasone (BD) after high-dose dexamethasone therapy. Marked improvement of anemia and elevated serum alkaline phosphatase levels was recognized. After 5 cycles of BD therapy, the patient achieved a stringent complete response according to International Myeloma Working Group Response Criteria. BD therapy might be a feasible and useful treatment option for IgD myeloma.

Key words: multiple myeloma, immunoglobulin D, bortezomib, stringent complete response, alkaline phosphatase, blood transfusion


Introduction

Immunoglobulin D (IgD) myeloma is a very rare subtype of myelomas, accounting for about 2% of all myelomas. Few case series are available for IgD myeloma, but it is generally recognized as having aggressive clinical behavior, such as osteolytic lesions, renal impairment, hypercalcemia, anemia, extramedullary plasmacytoma, and amyloidosis (1-4). Recently, myeloma survival has markedly improved by high-dose chemotherapy with autologous stem cell transplantation (SCT) (5), bortezomib (6), and immunomodulatory drugs, although reports concerning the treatments and responses of IgD myeloma are still limited (2-4). We report here a case of successful treatment of IgD myeloma with bortezomib and dexamethasone (BD) therapy.

Case Report

A 66-year-old woman was admitted to our hospital in September 2010 because of lumbago. The X-ray film revealed punched out lesions in the skull (Fig. 1A) and ribs, and a compression fracture in the lumbar (L) vertebra (Fig. 1B). Magnetic resonance imaging also showed a compression fracture of the L4 vertebra. Laboratory data were as follows: Hb 7.9 g/dL, compensated Ca 11.6 mg/dL, total protein 7.0 g/dL, albumin 3.8 g/dL, beta2-microglobulin 4.2 mg/L, and LDH 141 IU/L. Serum protein electrophoresis lacked an M-spike (Fig. 2A), urine protein was 3,284 mg/day, and Bence Jones protein kappa was recognized by immunoelectrophoresis of urine (Fig. 2B). IgD was 2,170 mg/dL (usually <9), whereas other Ig levels decreased (IgG 811 mg/dL, usual range: 870-1,700; IgA 61 mg/dL, usual range: 110-410; IgM 29 mg/dL, usual range: 46-260). Bone marrow aspirate revealed diffuse infiltration of neoplastic plasma cells (Fig. 3A). Flow cytometric analysis for neoplastic cells of CD 38 gating showed positive for MPC-1, CD45, and negative for 49e, suggesting that most of the neoplastic cells were intermediate differentiated cells. Conventional cytogenetic analysis showed 46,XX, and negative for 49e, suggesting that most of the neoplastic cells were intermediate differentiated cells. Conventional cytogenetic analysis showed 46,XX, and fluorescence in-situ hybridization (FISH) analyses for IgH-Bcl-1, IgH-FGFR3, IgH-C-MYC, del13, and del 17p13 were negative. Immunohistochemical staining of a bone marrow biopsy specimen showed that the tumor cells were positive for

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CD138, IgD, and kappa, and negative for lambda (Fig. 3B-F). Therefore, she was diagnosed with symptomatic IgD-kappa myeloma according to the International Myeloma Working Group criteria (7). Her clinical stage was II according to the International Staging system (8). Her performance status was 2 by Eastern Cooperative Oncology Group criteria.

She refused blood transfusion because of her beliefs, although her age made her a marginal candidate for first-line high-dose chemotherapy with autologous SCT. She was treated with BD therapy after one cycle of high-dose dexamethasone therapy, and administration of pamidronate. One cycle of BD therapy consisted of intravenous administration of bortezomib 1.3 mg/m², and dexamethasone 16 mg/body on day 1, 4, 8, 11, and was repeated every 21 days. Tumor lysis syndrome was not recognized. After BD therapy, improved anemia and marked elevation of serum alkaline phosphatase (ALP) were recognized (Fig. 4) in parallel with improved lumbago and remodeling of the trabecula of L vertebra (Fig. 1C).

After 5 cycles of BD therapy, the serum free light chain kappa/lambda ratio was 0.37 (range: 0.26-1.65) and flow cytometric analysis of the kappa/lambda ratio of neoplastic cells was normal by bone marrow aspirate. Therefore, she achieved stringent CR (sCR) according to the International Myeloma Working Group response criteria (9). After achieving sCR, she received 100 mg/day thalidomide orally as maintenance therapy. sCR has been maintained for 6 months.

**Discussion**

IgD multiple myeloma is rare, accounting for only 1-2% of all myelomas. Although few case series of retrospective analysis are available for IgD myeloma, it is generally recognized as having aggressive clinical behavior and a poor prognosis (1-4). In addition to its rarity, the poor prognosis might be due to the delayed precise diagnosis. Kuliszkwicz-Janus et al. pointed out the diagnostic difficulties because 40% of IgD myeloma lacks a monoclonal protein spike, and there are a variety of non-specific initial symptoms, such as arthritis and neurological symptoms, due to amyloidosis (1). In the present case, a typical monoclonal protein spike was not recognized by serum protein electrophoresis. Recently, many cytogenetic or molecular analyses have been accumulated related with the prognosis (10), and...
the Mayo Clinic in the United States has attempted risk-adapted therapy (11). On the other hand, Kim et al. reported that the prognosis of IgD myeloma remains poor, and the median overall survival of 75 patients with IgD myeloma was 18.5 months, compared with 50.1 months for all myelomas in a Korean multicenter retrospective analysis (2). Thus, the IgD subtype might be an independent risk factor at the present time.

Autologous SCT has been established as the first-line therapy for myeloma patients under 65 years old (5). This is the same as IgD myeloma, although the prognosis is poor compared with IgG, and IgA myelomas from the European Group for Blood and Marrow Transplantation Myeloma Database (12). In the present case, her age made her a marginal candidate for first-line autologous SCT; however, she refused a blood transfusion. Thus, we needed to select a less toxic therapeutic regimen. Bortezomib, known as a proteasome inhibitor, has been established as the first-line induction therapy with dexamethasone for all patients by National Comprehensive Cancer Network Guidelines for multiple

Figure 3. Neoplastic cells in the bone marrow. (A) May-Giemsa staining of bone marrow aspirates. Neoplastic cells with three nuclei were recognized. (B) Diffuse invasion of neoplastic cells was recognized from the bone marrow biopsy specimen (Hematoxylin and Eosin staining, original magnification ×400). (C) Staining with CD138. The cytoplasm of neoplastic cells was strongly positive for CD138 (original magnification ×630). (D) Immunoglobulin D staining. The cytoplasm of neoplastic cells was strongly positive (original magnification ×630). (E) Staining with immunoglobulin kappa. The cytoplasm of neoplastic cells was strongly positive for kappa (original magnification ×630). (F) Staining with immunoglobulin lambda. Neoplastic cells were negative (original magnification ×630).
myeloma (13). BD therapy is less toxic in hematological suppression and has a high response rate, so it was used for this patient. Few reports have discussed whether a bortezomib-containing regimen might be useful for IgD myeloma (3, 14). Fortunately, the patient achieved sCR after 5 cycles of BD therapy without blood transfusion. Furthermore, she has been receiving thalidomide therapy as maintenance therapy. Thalidomide is less toxic in hematological suppression than lenalidomide. Thalidomide monotherapy is well-known to be ineffective for myeloma, and it causes worse cytogenetic abnormalities, including del13 (15, 16). Fortunately, in the present case, cytogenetic abnormality did not occur.

Interestingly, marked serum ALP level elevation was recognized. Bortezomib was reported to activate osteoblast progenitors and osteoblasts by increased transcription factor Runx2/Cbfa1 activity (17). Furthermore, it is reported that the elevated serum ALP level is associated with the response of bortezomib (18, 19). Marked improvement of lumbago and remodeling of trabecula of lumbar vertebra were recognized in parallel with the elevated serum ALP in the present case.

Although reports concerning the treatment and responses of IgD myeloma remain limited, we successfully achieved sCR by BD therapy without the need for SCT and blood transfusion. BD therapy might be a feasible and useful treatment option for IgD myeloma, although further studies are warranted.

The authors state that they have no Conflict of Interest (COI).

References


