[CASE REPORT]

Successful Autologous Hematopoietic Stem Cell Transplantation Followed by Bortezomib Maintenance in a Patient with Relapsed CD138-low Multiple Solitary Plasmacytomas Harboring a 17p Deletion

Hiroaki Kitamura¹, Yasushi Kubota^{1,2}, Kyosuke Yamaguchi¹, Kazuharu Kamachi¹,
Atsujiro Nishioka¹, Masako Yokoo¹, Takero Shindo¹, Toshihiko Ando¹,
Kensuke Kojima¹ and Shinya Kimura¹

Abstract:

Solitary bone plasmacytoma (SBP) tends to progress to multiple myeloma (MM); however, progression to multiple solitary plasmacytomas (MSP) is rare. We report a case of CD138-low MSP with 17p deletion in a patient with relapsed SBP. 17p deletion is associated with a poor outcome in patients with MM, and the low expression of CD138 in myeloma cells is associated with drug resistance and a poor prognosis. The patient was successfully treated with bortezomib plus dexamethasone induction therapy and autologous hematopoietic stem cell transplantation followed by bortezomib maintenance therapy. Consequently, bortezomib treatment was stopped and a stringent complete response has been maintained.

Key words: multiple myeloma, plasmacytoma, CD138, proteasome inhibitor, p53, autologous hematopoietic stem cell transplantation

(Intern Med 57: 855-860, 2018)

(DOI: 10.2169/internalmedicine.9446-17)

Introduction

Solitary plasmacytoma accounts for 5-10% of all plasma cell neoplasms and occurs more commonly in men than in women (2:1) (1). The International Myeloma Working Group classifies plasmacytomas into solitary bone plasmacytoma (SBP), extramedullary plasmacytoma, and multiple solitary plasmacytomas (MSP) (2). MSP occurs in up to 5% of patients with SBP (2). Radical radiotherapy with or without surgery is recommended for the treatment of SBP; however, an effective treatment strategy has not been established for patients with MSP (2, 3). Autologous hematopoietic stem cell transplantation (auto-HSCT) was previously shown to be effective for improving overall survival in patients with high-risk plasmacytoma (4). Patients who were considered to be at high risk of evolution to multiple myeloma

(MM) were included in the study; however, a risk classification based on a cytogenetic analysis was not used (4). Radiotherapy plus adjuvant chemotherapy and the use of novel-agents have not improved survival in patients with solitary plasmacytoma (5).

17p deletion is a predictor of short survival in patients with MM (6). Recent studies suggest that the low expression of CD138 in myeloma cells is associated with an immature phenotype, drug resistance, and a poor prognosis (7, 8). However, due to the rarity of plasmacytoma, no definitive prognostic factors with genetic abnormalities resembling MM have been identified to date and no novel agent-based maintenance therapies after auto-HSCT have shown efficacy in the treatment of plasmacytoma.

We herein report a case of relapsed CD138-low MSP with 17p deletion. The patient received bortezomib plus dexamethasone induction therapy and auto-HSCT followed by

¹Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Japan and ²Department of Transfusion Medicine, Saga University Hospital, Japan

Received: May 8, 2017; Accepted: July 18, 2017; Advance Publication by J-STAGE: November 20, 2017

Correspondence to Dr. Yasushi Kubota, kubotay@cc.saga-u.ac.jp

Figure 1. The findings of solitary plasmacytoma at the first relapse. **A:** PET-CT showed the increased accumulation of ^{18}F -FDG in the mass in the right chest (arrow). **B:** Hematoxylin and Eosin staining of the mass (magnification 400 $\times$). **C:** Immunohistochemical staining with anti-CD38 antibody (magnification 400 $\times$). **D:** The characterization of the cells by flow cytometry. The CD38 $^{+}$ gated cells were subjected to two-color flow cytometry using antibodies specific for CD19 and CD56 (left plot), CD138 and CD20 (middle plot), or intracytoplasmic lambda and kappa (right plot). The CD38 $^{+}$ gated cells were CD19 $^{-}$ CD20 $^{-}$ CD138 $^{\text{low}}$ CD56 $^{+}$.

bortezomib maintenance therapy, and a stringent complete response (sCR) was achieved.

Case Report

A 55-year-old man presented to our hospital with a mass in the right anterior chest. He was diagnosed with IgG- λ type solitary plasmacytoma of the right third rib at 44 years of age and received radiotherapy. At presentation, his IgG level was slightly elevated (2,091 mg/dL, normal range: 861-1,747 mg/dL), and IgG- λ type M protein was detected by immunoelectrophoresis. ^{18}F -fluorodeoxyglucose (^{18}F -FDG)-positron emission tomography/computed tomography (PET/CT) showed the increased accumulation of ^{18}F -FDG in the mass on the right fifth rib (SUV max: 10.36, Fig. 1A). The mass was completely resected and the patient was diagnosed with a relapse of IgG- λ type plasmacytoma (Fig. 1B and C). Flow cytometry showed that CD38-gated cells were positive for CD56 and lambda, but negative for CD19, CD20, CD138, and kappa (Fig. 1D). A chromosomal analysis was difficult to perform because of the low proliferative rate of cells. We did not perform a fluorescence *in situ* hybridization (FISH) analysis to detect t(4;14), t(14;16) and 17p deletion. Bone marrow aspiration and biopsy revealed no evidence of clonal myeloma cells.

At 2 years after resection, the patient presented with pain

in the bilateral lower regions of the rib, and blood tests showed an elevated level of IgG (4,235 mg/dL). PET/CT showed the increased accumulation of ^{18}F -FDG in multiple lymph nodes (Fig. 2A). A right axillary lymph node biopsy was performed and CD138-low IgG- λ type plasmacytoma was histopathologically diagnosed (Fig. 2B-D). Flow cytometry showed the increased expression of CD19. A FISH analysis revealed 17p deletion (Fig. 2E); fusion signals of t(4;14) and t(14;16) were not detected. Bone marrow aspiration and biopsy revealed no evidence of clonal myeloma cells. Based on these findings, a clinical diagnosis of relapsed CD138-low MSP with the deletion of 17p was made.

The patient was treated with bortezomib plus dexamethasone induction therapy [BD: bortezomib (1.3 mg/m 2 on days 1, 4, 8, and 11, by intravenous infusion) and dexamethasone (20 mg/day, orally on days 1, 2, 4, 5, 8, 9, 11, and 12 for cycles 1-2; and days 1, 2, 4, and 5 for cycles 3-8 in a 3 week cycle)] (9, 10) and a partial response (PR) was achieved after four cycles. Thereafter, progenitor cell mobilization with granulocyte colony-stimulating factor alone and progenitor cell apheresis were successfully performed. However, at 1 month after apheresis, he noticed a soft mass of 10 cm in the left lateral scapula. Contrast CT showed a flat cyst with peripheral enhancement in the left lower scapula, which was suspected to be an exacerbation presenting as a bursitis-like lesion (Fig. 3A). A small amount of bloody

Figure 2. The findings of relapsed plasmacytoma at the second relapse. A: The accumulation of ^{18}F -FDG in multiple lymph nodes. B: May-Giemsa staining of a stamped specimen of the lymph node (magnification 400 $\times$). C: Hematoxylin and Eosin staining of the lymph node (magnification 400 $\times$). D: Characterization of the cells by flow cytometry. The CD38 $^{+}$ gated cells were subjected to two-color flow cytometry using antibodies specific for CD19 and CD56 (left plot), CD138 and CD20 (middle plot), or intracytoplasmic lambda and kappa (right plot). The CD38 $^{+}$ gated cells were CD19 $^{+}$ CD20 $^{-}$ CD138 $^{\text{low}}$ CD56 $^{+}$. E: 17p deletion was identified by interphase FISH. FISH with a p53 probe on the interphase nuclei. No p53 signal (red) was detected.

Figure 3. A bursitis-like lesion emerged after four courses of BD therapy. A: Contrast-enhanced CT showed a flat cyst with peripheral enhancement in the left lower scapula (arrow). B: May-Giemsa staining of cytological specimens from a bursitis-like lesion (magnification 400 $\times$). C: Anti-CD38 staining of cytological specimens from a bursitis-like lesion (magnification 400 $\times$).

fluid was aspirated. The fluid showed a white blood cell count of $0.1 \times 10^9/\text{L}$ with 17% plasma cells, which were positive for CD38 on immunohistochemical staining (Fig. 3B and C). The patient received an additional four cycles of BD therapy without a further exacerbation of the plasmacytoma. The results of a physical examination before transplantation were unremarkable. His serum IgG level de-

creased to 599 mg/dL; IgG- λ type M protein was still detected on serum immunoelectrophoresis. The serum free light chain ratio was within the normal limits at 0.81 (normal range: 0.26-1.65). His response before transplantation was classified as a PR. Subsequently, high-dose melphalan ($100 \text{ mg}/\text{m}^2$ for 2 days) was administered followed by auto-HSCT; no severe adverse events were observed. IgG- λ type

Figure 4. The clinical course before and after autologous hematopoietic stem cell transplantation. Immunoglobulin G (IgG) levels and the free light chain (κ/λ) ratio, the results of immunoelectrophoresis, and immunofixation electrophoresis throughout the clinical course are shown. BD: bortezomib and dexamethasone, HD-Mel: high dose-melphalan, auto-HSCT: autologous hematopoietic stem cell transplantation, IEP: immunoelectrophoresis, IFE: immunofixation electrophoresis, D: detected, N/D: not detected

M protein was still detected by immunoelectrophoresis after auto-HSCT. Thus, his response after auto-HSCT was classified as a PR.

He was treated with bortezomib (1.0 mg/m² once in a 2 week cycle by subcutaneous infusion) as post-transplant maintenance therapy starting at 3 months after auto-HSCT. At 2 years after auto-HSCT, IgG- λ type M protein was no longer detected by immunofixation electrophoresis and the serum free light chain ratio was within the normal range. PET/CT showed no abnormal accumulation of ¹⁸F-FDG (data not shown). Thereafter, bortezomib was administered once a month for another year. At 3 years after auto-HSCT, IgG- λ type M protein was not detected by immunofixation electrophoresis and the serum free light chain ratio was within normal limits (Fig. 4). In the maintenance phase, he experienced grade 1 taste alteration and grade 1 peripheral sensory neuropathy as adverse events. Consequently, bortezomib treatment was stopped and an sCR has been maintained without recurrence for 8 months.

Discussion

We report a case of relapsed MSP. The expression of CD138 was low and 17p deletion was detected. The patient

received BD induction therapy and high-dose melphalan followed by auto-HSCT. Biweekly bortezomib maintenance therapy was started at 3 months after transplantation, and an sCR was achieved and maintained.

SBP tends to progress to MM at a rate of 65-84% in 10 years (1). The present patient did not progress to MM but experienced a relapse of MSP. There are few organized reports describing the risk factors for progression to multiple plasmacytomas. In patients with MM, 17p deletion is relatively rare at the time of the diagnosis, whereas its incidence increases with disease progression (11). The presence of 17p deletion is associated with a significantly shorter overall survival in myeloma patients. In the era of conventional chemotherapy, the median overall survival in patients with and without 17p deletion is reported to be 13.9 months and 38.7 months, respectively (12). Bortezomib-based induction therapy has not improved the outcome of MM patients with 17p deletion (13). However, the prognosis of plasmacytoma patients with 17p deletion remains unclear. In the present case, the presence or absence of 17p deletion could not be determined at the initial diagnosis or at the time of the first relapse, but was detected at the second relapse. Since the second relapse occurred in a short period of time, 17p deletion was presumed to have emerged between the first and second

relapse.

An analysis of the plasmacytoma of the present patient at both the first and second relapse showed that the level of CD138 expression was low. CD138 is a characteristic marker of plasma and myeloma cells. CD138 mediates the adhesion of myeloma cells to the bone marrow stromal matrix (14). In the present case, we hypothesized that the SBP progressed to multiple plasmacytomas with an unusual manifestation of a bursitis-like lesion because of the low expression of CD138. Pre-plasma cells (CD19⁺CD138⁺) similar to the cell surface phenotype observed at the first relapse of the present case show drug resistance that is up to 300-fold higher than that of the CD19⁺CD138⁺ plasma cell population (7). In the present case, flow cytometry of tumor cells from lymph nodes at the second relapse revealed CD19⁺CD138^{low} cells, which show immature characteristics after they acquire the expression of CD19. Although the presence and characterization of MM stem cells or myeloma-initiating cells has been controversial, several laboratories have identified peripheral blood clonal CD19⁺ cells, which may be MM stem cells or the tumor-propagating cell responsible for relapse (15-17). In the present patient, the CD19⁺ cells that persisted after the resection of the SBP at the time of the first relapse might have proliferated in the form of multiple plasmacytomas. Furthermore, the expression of CD19 in MM cells has been associated with shorter progression free and overall survival (18, 19). Inoue et al. reported the clinical significance of decreased CD138 expression in MM. A decrease in CD138⁺ levels is associated with a poor prognosis, even during the course of treatment (20).

Recent reports show that the administration of bortezomib before and after transplantation improves overall and progression-free survival in MM patients with 17p deletion. Long-term maintenance therapy with bortezomib after transplantation is recommended for MM patients with 17p deletion (21). The low expression of CD138 and 17p deletion predicted a poor prognosis in the present patient. Hence, we decided to perform auto-HSCT and to administer post-transplantation bortezomib maintenance therapy for a long period. An sCR was achieved without recurrence despite the presence of 17p deletion. Bortezomib protects p53 from degradation and promotes apoptosis (22). Although the FISH analysis showed the deletion of 17p, bortezomib may have induced p53-independent apoptosis in the present case (23). Lenalidomide was another treatment option for maintenance therapy after transplantation in the patient at that time. However, *in vitro* experiments indicate that CD138-low myeloma cells may be resistant to lenalidomide (8). Moreover, lenalidomide is not effective in overcoming the poor prognosis of MM in patients with 17p deletion (24). A new agent, carfilzomib monotherapy, does not improve the overall survival of patients with 17p deletion (25).

In the present study, we reported the case of a patient with relapsed MSP in whom an sCR was successfully

achieved after auto-HSCT followed by bortezomib maintenance despite the presence of poor prognostic factors. Auto-HSCT followed by bortezomib maintenance therapy is tolerable, and a deep response may improve the outcome of patients with relapsed plasmacytoma with poor prognostic factors. It is important to clarify the risk classification of plasmacytoma. Further clinical studies are needed to establish a suitable treatment strategy for multiple plasmacytomas.

Author's disclosure of potential Conflicts of Interest (COI).

Shinya Kimura: Research funding, Celgene.

References

1. Kilciksiz S, Karakoyun-Celik O, Agaoglu FY, Haydaroglu A. A review for solitary plasmacytoma of bone and extramedullary plasmacytoma. *ScientificWorld Journal* **2012**: 895765, 2012.
2. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol* **121**: 749-757, 2003.
3. Soutar R, Lucraft H, Jackson G, et al. Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma. *Br J Haematol* **124**: 717-726, 2004.
4. Jantunen E, Koivunen E, Putkonen M, Siitonen T, Juvonen E, Nousiainen T. Autologous stem cell transplantation in patients with high-risk plasmacytoma. *Eur J Haematol* **74**: 402-406, 2005.
5. Katodritou E, Terpos E, Symeonidis AS, et al. Clinical features, outcome, and prognostic factors for survival and evolution to multiple myeloma of solitary plasmacytomas: a report of the Greek myeloma study group in 97 patients. *Am J Hematol* **89**: 803-808, 2014.
6. Vincent Rajkumar S. Multiple myeloma: 2014 Update on diagnosis, risk-stratification, and management. *Am J Hematol* **89**: 999-1009, 2014.
7. Chaidos A, Barnes CP, Cowan G, et al. Clinical drug resistance linked to interconvertible phenotypic and functional states of tumor-propagating cells in multiple myeloma. *Blood* **121**: 318-328, 2013.
8. Kawano Y, Fujiwara S, Wada N, et al. Multiple myeloma cells expressing low levels of CD138 have an immature phenotype and reduced sensitivity to lenalidomide. *Int J Oncol* **41**: 876-884, 2012.
9. Jagannath S, Richardson PG, Barlogie B, et al. Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. *Haematologica* **91**: 929-934, 2006.
10. Harousseau JL, Attal M, Leleu X, et al. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study. *Haematologica* **91**: 1498-1505, 2006.
11. Chng WJ, Price-Troska T, Gonzalez-Paz N, et al. Clinical significance of TP53 mutation in myeloma. *Leukemia* **21**: 582-584, 2007.
12. Drach J, Ackermann J, Fritz E, et al. Presence of a p53 gene deletion in patients with multiple myeloma predicts for short survival after conventional-dose chemotherapy. *Blood* **92**: 802-809, 1998.
13. Avet-Loiseau H, Leleu X, Roussel M, et al. Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p). *J Clin Oncol* **28**: 4630-4634, 2010.
14. O'Connell FP, Pinkus JL, Pinkus GS. CD138 (syndecan-1), a plasma cell marker immunohistochemical profile in hematopoietic

- and nonhematopoietic neoplasms. *Am J Clin Pathol* **121**: 254-263, 2004.
15. Rasmussen T, Haaber J, Dahl IM, et al. Identification of translocation products but not K-RAS mutations in memory B cells from patients with multiple myeloma. *Haematologica* **95**: 1730-1737, 2010.
 16. Rasmussen T, Jensen L, Johnsen HE. The CD19 compartment in myeloma includes a population of clonal cells persistent after high-dose treatment. *Leuk Lymphoma* **43**: 1075-1077, 2002.
 17. Hajek R, Okubote SA, Svachova H. Myeloma stem cell concepts, heterogeneity and plasticity of multiple myeloma. *Br J Haematol* **163**: 551-564, 2013.
 18. Mateo G, Montalban MA, Vidriales MB, et al. Prognostic value of immunophenotyping in multiple myeloma: a study by the PETHEMA/GEM cooperative study groups on patients uniformly treated with high-dose therapy. *J Clin Oncol* **26**: 2737-2744, 2008.
 19. Paiva B, Puig N, Cedena MT, et al. Differentiation stage of myeloma plasma cells: biological and clinical significance. *Leukemia* **31**: 382-392, 2017.
 20. Inoue J, Ikeda M, Shingaki S, et al. The clinical significance of decrease in CD138 positive cell ratio in multiple myeloma. *Rinsho Ketsueki (The Japanese Journal of Clinical hematology)* **56**: 2311-2317, 2015 (in Japanese, Abstract in English).
 21. Neben K, Lokhorst HM, Jauch A, et al. Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p. *Blood* **119**: 940-948, 2012.
 22. Teoh PJ, Chng WJ. p53 abnormalities and potential therapeutic targeting in multiple myeloma. *Biomed Res Int* **2014**: 717919, 2014.
 23. Pandit B, Gartel AL. Proteasome inhibitors induce p53-independent apoptosis in human cancer cells. *Am J Pathol* **178**: 355-360, 2011.
 24. Chang H, Jiang A, Qi C, Trieu Y, Chen C, Reece D. Impact of genomic aberrations including chromosome 1 abnormalities on the outcome of patients with relapsed or refractory multiple myeloma treated with lenalidomide and dexamethasone. *Leuk Lymphoma* **51**: 2084-2091, 2010.
 25. Jakubowiak AJ, Siegel DS, Martin T, et al. Treatment outcomes in patients with relapsed and refractory multiple myeloma and high-risk cytogenetics receiving single-agent carfilzomib in the PX-171-003-A1 study. *Leukemia* **27**: 2351-2356, 2013.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).