Bence-Jones Protein \( \lambda \)-type Multiple Myeloma Patient Withdrawn from Maintenance Hemodialysis after Long-term Bortezomib and Dexamethasone Therapy

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Abstract

The effectiveness of bortezomib treatment for multiple myeloma (MM) is well established. However, the protocol by which maintenance therapy using bortezomib should be continued for myeloma patients requiring regular hemodialysis remains to be established. We herein report a case of MM with severe renal insufficiency requiring hemodialysis for nearly 30 months which was finally withdrawn from renal replacement therapy during monthly maintenance treatment with bortezomib and dexamethasone for two years. The details of this case are essential for establishing clinical guidelines for applying intermittent low-frequency bortezomib therapy in dialysis-dependent myeloma patients.

Key words: multiple myeloma, maintenance therapy, bortezomib, hemodialysis, fibrosis, myofibroblast

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Introduction

Bortezomib, a derivative of boronic acid, is a selective and reversible proteasome inhibitor. Its effect on cell growth inhibition has been confirmed in more than 60 human cancer cell lines in vitro (1). In particular, bortezomib is effective for inhibiting the growth of myeloma cells (2, 3). With regard to representative molecular mechanisms, bortezomib induces myeloma cell apoptosis via the inactivation of NF-\( \kappa \)B by blocking I-\( \kappa \)B degradation and inhibits the production of adhesion molecules, e.g., intracellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1), in myeloma cells preventing its interaction with bone marrow stromal cells (4), which is crucial for the development of multiple myeloma (MM).

The usefulness of bortezomib was first clinically proven in refractory MM patients (5) and subsequently in previously untreated MM patients (6). Several clinical studies using bortezomib for MM maintenance therapy have revealed that it is relatively well tolerated with long-term use (7, 8).

Induction therapy using bortezomib has also been applied in dialysis-dependent MM patients, and it has been reported that some patients have been successfully removed from renal replacement therapy (9-12). However, the protocol by which maintenance therapy using bortezomib for dialysis-dependent MM should be continued is undetermined, and the influence of the long-term use of bortezomib on dialysis-dependent MM patients is unknown.

The clinical course of the present case may help in establishing maintenance guidelines for dialysis-dependent MM patients. In addition, this case suggests the novel therapeutic application of bortezomib for preventing advanced renal failure, possibly by preventing subsequent renal fibrosis after acute kidney injury.

Case Report

A 61-year-old Japanese woman with no medical history of kidney disease was referred to our department with severe renal dysfunction. The patient had developed high blood pressure (219/119 mmHg), severe bilateral leg edema,
The serum creatinine and no nephrotoxic drugs were prescribed for this patient. During the exacerbation period, a 5 kg body weight gain, and oliguria over the past few weeks prior to admission. Notable laboratory findings on admission were as follows. The serum creatinine and β2-microglobulin (β2-MG) levels were greatly increased at 15.5 mg/dL and 30.8 mg/dL, respectively. The serum uric acid level was elevated at 10.2 mg/dL, and the urine β2-MG and N-acetyl-β-glucosaminidase (NAG) levels were elevated at 27,392 μg/L and 9.2 U/L, respectively (Table). Abdominal ultrasonography revealed that the kidneys were within the normal size range, suggesting that the patient’s kidney failure was not chronic.

A bone marrow aspiration examination showed an increase in atypical plasma cells of up to 15% and λ-positive findings on immunostaining (Fig. 1B). A cytogenetic analysis of bone marrow showed a normal karyotype. A percutaneous kidney biopsy was performed to determine the histological diagnosis of the patient’s renal failure. The specimen comprised bortezomib at a dose of 2 mg (i.v.) and dexamethasone 33 mg (i.v.) on days 1, 4, 8, 11, and dexamethasone 33 mg (i.v.) on days 1, 2, 4, 5, 8, 9, 11, 12, followed by a drug-free period until day 21: defined as one cycle.

After four cycles of induction therapy, a urine immunofixation electrophoresis assay detected no M-protein, and the serum free light chain ratio became normal. The ab-

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Table. Laboratory Data on Admission.

| Parameter          | Value          |
|--------------------|----------------|
| Hemoglobin         | 11.8 g/dL      |
| White blood cells  | 11,900 μL      |
| Platelets          | 26.8 × 10^4/μL |
| Total protein      | 6.7 g/dL       |
| Albumin            | 3.3 g/dL       |
| Uric acid          | 10.2 mg/dL     |
| Urea nitrogen      | 120.6 mg/dL    |
| Creatinine         | 15.46 mg/dL    |
| eGFR               | 2.2 ml/min/1.73m² |
| β2-microglobulin   | 30.2 mg/L      |
| Calcium            | 8.7 mg/dL      |
| Phosphorus         | 8.6 mg/dL      |
| Sodium             | 143 mEq/L      |
| Potassium          | 5.8 mEq/L      |
| Chloride           | 101 mEq/L      |
| Glucose            | 97 mg/dL       |
| Hemoglobin A1c     | 5.40 %         |
| C-reactive protein | 2.65 mg/dL     |
| IgG                | 523 mg/dL      |
| IgA                | 70 mg/dL       |
| IgM                | 20 mg/dL       |
| C3                 | 114 mg/dL      |
| C4                 | 36 mg/dL       |
| Anti-nuclear antibody | (-)          |
| Anti-GBM antibody  | < 10           |
| MPO-ANCA           | < 10           |
| PR3-ANCA           | < 10           |
| Urine-protein      | 2+             |
| Urine-occult blood | ±              |
| Urine-NAG          | 9.2 U/L        |
| Urine-protein electrophoresis | BJP-λ (+)  |

eGFR: estimated glomerular filtration rate, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3 anti-neutrophil cytoplasmic antibody, GBM: glomerular basement membrane, NAG: N-acetyl-β-glucosaminidase

Following the initiation of hemodialysis three times per week, the patient was treated with high-dose dexamethasone; however, it was not effective. We then started induction therapy using bortezomib and dexamethasone (BD) [bortezomib 2 mg (=1.3 mg/m²) (i.v.) on days 1, 4, 8, 11, and dexamethasone 33 mg (i.v.) on days 1, 2, 4, 5, 8, 9, 11, 12, followed by a drug-free period until day 21: defined as one cycle].

With the patient’s consent, we continued the BD therapy once a month for MM maintenance therapy. This treatment comprised bortezomib at a dose of 2 mg (i.v.) and dexamethasone at a dose of 33 mg (i.v.) on day 1 followed by a drug-free period for one month (monthly BD therapy). During the monthly BD therapy, the patient continued to show a slow renal recovery, and the hemodialysis regimen was decreased to twice a week (Fig. 2A). In the middle three weeks prior to admission. During the exacerbation period, no nephrotoxic drugs were prescribed for this patient.

Notable laboratory findings on admission were as follows. The serum creatinine and β2-microglobulin (β2-MG) levels were greatly increased at 15.5 mg/dL and 30.8 mg/dL, respectively. The serum uric acid level was elevated at 10.2 mg/dL, and the urine β2-MG and N-acetyl-β-glucosaminidase (NAG) levels were elevated at 27,392 μg/L and 9.2 U/L, respectively (Table). Abdominal ultrasonography revealed that the kidneys were within the normal size range, suggesting that the patient’s kidney failure was not chronic.

A bone marrow aspiration examination showed an increase in atypical plasma cells of up to 15% and λ-positive findings on immunostaining (Fig. 1B). A cytogenetic analysis of bone marrow showed a normal karyotype. A percutaneous kidney biopsy was performed to determine the histological diagnosis of the patient’s renal failure. The specimen included 18 glomeruli, none of which showed any global sclerosis. A moderate degree of interstitial edema, interstitial cellular infiltration and mild tubular atrophy were observed; however, interstitial fibrosis was not obvious at that point. Infiltrating cells in the renal interstitium mainly consisted of lymphocytes and plasma cells with no atypicality. Immunostaining revealed that λ-positive casts were positive in the patient’s tubules (Fig. 1C) with no pathological signs of amyloidosis on Congo red staining. The cause of renal failure was diagnosed as BJP-λ-type MM stage 3 based on the International Staging System criteria (13).

Following the initiation of hemodialysis three times per week, the patient was treated with high-dose dexamethasone; however, it was not effective. We then started induction therapy using bortezomib and dexamethasone (BD) [bortezomib 2 mg (=1.3 mg/m²) (i.v.) on days 1, 4, 8, 11, and dexamethasone 33 mg (i.v.) on days 1, 2, 4, 5, 8, 9, 11, 12, followed by a drug-free period until day 21: defined as one cycle].

After four cycles of induction therapy, a urine immunofixation electrophoresis assay detected no M-protein, and the serum free light chain ratio became normal. The absence of BJP-λ persisted for more than six weeks, and atypical λ-positive plasma cells were rarely detected (0.6%) on the second bone marrow aspiration examination (Fig. 2), suggesting that the patient’s MM achieved a stringent complete response according to the International Myeloma Working Group response criteria (14). The patient’s urine volume gradually increased, and no serious clinical signs of BD-related adverse effects were observed (e.g., interstitial pneumonitis, peripheral neuropathy, thrombocytopenia). Therefore, we continued the induction therapy. After a total of eight cycles of induction BD therapy, the patient’s predialysis serum creatinine level continued to be high at 6.5 mg/dL (Fig. 2A), the urine β2-MG level exceeded the upper limit at 85,000 μg/L (Fig. 2B) and she remained dependent on maintenance hemodialysis therapy three times per week.

With the patient’s consent, we continued the BD therapy once a month for MM maintenance therapy. This treatment comprised bortezomib at a dose of 2 mg (i.v.) and dexamethasone at a dose of 33 mg (i.v.) on day 1 followed by a drug-free period for one month (monthly BD therapy). During the monthly BD therapy, the patient continued to show a slow renal recovery, and the hemodialysis regimen was decreased to twice a week (Fig. 2A). In the middle three
weeks during the twice a week hemodialysis period, around the 12th monthly BD cycle, in which the predialysis serum creatinine level was approximately 5 mg/dL (Fig. 2A), the mean interdialytic weight gain was 2.7±0.18 kg (n=6), suggesting that the patient’s renal recovery was not adequate to be independent of renal replacement therapy at that time.

We further continued the monthly BD therapy, and the timing of hemodialysis was decreased to once a week (Fig. 2A). The patient’s predialysis serum creatinine level decreased to 3.7 mg/dL; we therefore discontinued the hemodialysis and monthly BD therapy. In total, she received eight cycles of induction BD therapy followed by 21 months of monthly BD therapy without any serious clinical adverse effects.

Almost 1.5 years after the discontinuation of hemodialysis and monthly BD therapy, the patient’s serum creatinine level has remained stable at around 2.7 mg/dL (Fig. 2A), the urine β2-MG level decreased to 17,422 μg/L (Fig. 2B) and the MM activity is currently maintained with a stringent complete response. Additionally, the patient has been withdrawn from regular erythropoiesis-stimulating agent treatment. The patient’s hemoglobin level has also been main-
without erythropoiesis-stimulating agent therapy, indicating
that the patient’s renal interstitial fibrosis was also amelio-
rated during the nearly two years of monthly BD therapy.

tained at over 12 g/dL with a sufficient reticulocyte count,
Discussion

This report summarizes the clinical course of a rare MM patient that was successfully withdrawn from regular hemodialysis after long-term maintenance therapy with BD. High-dose dexamethasone single-agent therapy for MM was not very effective in this case; therefore, the satisfactory clinical result was most likely induced by bortezomib. We note two important issues in the clinical course of the current case. First, long-term monthly maintenance BD therapy was effective and tolerable in this dialysis-dependent MM patient. Second, monthly BD therapy produced a very slow but continuous recovery in the renal function after achieving a complete response to MM.

Previous clinical studies have reported several dialysis-dependent MM cases withdrawn from renal replacement therapy using bortezomib-combined therapy. However, in almost all of these cases, a sufficient renal recovery independent of renal replacement therapy was acquired during several cycles of induction therapy using bortezomib (9-12), suggesting the renal recovery in these patients was more likely attained as a result of a natural release from the causative disease and related complications. To the best of our knowledge, the present case is the first report of a patient with MM to be withdrawn from renal replacement therapy after long-term maintenance BD therapy. The details of this case might be helpful in establishing initial clinical guidelines for the application of long-term bortezomib use as a maintenance therapy for dialysis-dependent MM patients. How to use bortezomib for maintenance MM therapy remains unclear, and long-term maintenance bortezomib therapy has rarely been used in dialysis-dependent patients to date. Therefore, the details and the successful clinical results of this case, in which long-term maintenance BD therapy was accomplished in a low-frequency manner for a dialysis-dependent MM patient, may provide a good initial reference.

An interesting observation worth considering is why the very slow renal recovery continued in this patient. It was positively observed that the MM disease activity was maintained in a complete response for a long time by the maintenance therapy, although this may not be deterministic of the good clinical result. We hypothesized that the monthly maintenance BD therapy prevented renal interstitial fibrosis from subsequently progressing following paraprotein-induced sub-acute renal injury. Indeed, the renal recovery continued together with a recovery in erythropoiesis. Importantly, several preclinical studies have demonstrated that bortezomib affects tissue fibrosis. For example, bortezomib prevents bleomycin-induced experimental dermal fibrosis in mice (15). In addition, bortezomib ameliorated liver fibrosis with a significant reduction of the α-smooth muscle actin expression in a N-nitrosodimethylamine-induced liver fibrosis rat model (16). In a renal in vitro investigation, MG132 (an experimental proteasome inhibiting agent) blocked the TGFβ-induced transformation of renal fibroblast NRK49F cells to myofibroblast cells (17), which express extracellular matrix and α-smooth muscle actin and play a key role in the progression of renal fibrosis (18). These preclinical observations support our hypothesis that bortezomib ameliorated the subsequent renal fibrosis in the present case. We regretfully did not check the urine β2-MG and NAG levels frequently; however, the time series of these values supports our hypothesis (Fig. 2B). We suggest that bortezomib may be effective in preventing subsequent renal interstitial fibrosis regardless of the cause.

It is desirable that numerous MM cases in which renal replacement therapy is not removed despite MM remission after standard induction BD therapy are recruited for assessments in randomized controlled trials with or without low-frequency maintenance BD therapy. It will be of interest to investigate the effects of bortezomib on the molecular mechanisms of renal fibrosis progression in experimental renal failure models.

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

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