Light Chain Deposition Disease in an Older Adult Patient Successfully Treated with Long-term Administration of Bortezomib, Melphalan and Prednisone

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Abstract

A 70-year-old woman was admitted to our hospital because of fatigue and renal dysfunction and was diagnosed with light chain deposition disease (LCDD) with multiple organ involvement (kidney, thyroid gland, heart and eyes). After chemotherapy with bortezomib, cyclophosphamide and dexamethasone, hepatobiliary enzyme levels increased abruptly. A liver biopsy showed light chain deposition in Disse spaces. After two years of treatment with bortezomib, melphalan and prednisone (VMP) administered at shorter intervals relative to regular cycles, the patient showed a hematological and organ response. This case indicates that a relatively low dose intensity VMP regimen is preferable for elderly patients with LCDD with multiple organ involvement.

Key words: cardiac involvement, liver involvement, multiple myeloma, ocular involvement, VMP therapy

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Introduction

Light chain deposition disease (LCDD) is a systemic disorder characterized by non-amyloid deposition of monoclonal light chain immunoglobulins in various organs (1). The clinical manifestation depends on the organs in which the light chains are deposited. This disease affects the kidney most frequently, presenting as proteinuria, nephrotic syndrome and renal failure. However, it can also involve other organs such as nerve fibers, lymph nodes, bone marrow, spleen, pancreas, thyroid gland, submandibular gland, adrenal glands, heart, lung, gastrointestinal tract and liver (2). The rate of LCDD complication is reported to be 58% for patients with multiple myeloma (3). Based on the production of monoclonal immunoglobulin light chains by abnormal plasma cells, various chemotherapeutic regimens similar to those adopted for multiple myeloma have been employed (4). However, a standard therapy has not been established because of the rare incidence of LCDD. Additionally, the long-term benefits of novel agents remain to be confirmed.

We herein present a case of an elderly patient with LCDD involving multiple organs. The patient showed a very good partial response characterized by lowered light chain levels in the affected organs following long-term administration of bortezomib, melphalan and prednisone (VMP) at a reduced dose intensity. Furthermore, the patient experienced improved renal and cardiac function and visual acuity.
Case Report

A 70-year-old woman was admitted to our hospital with fatigue, microscopic hematuria, proteinuria and renal dysfunction. Six months before the admission, she was first diagnosed with microscopic hematuria and proteinuria with an almost normal renal function. She did not have a family history of collagen-vascular disease, kidney disease or malignancy or a history of hypertension, diabetes mellitus or other diseases that cause renal failure.

On admission, she was alert, with a blood pressure of 136/72 mmHg, heart rate of 86 bpm and body temperature of 36.8°C. The palpebral conjunctiva was anemic. There was no skin rash, purpura or leg edema. Laboratory tests showed: leukocyte count 5,640/μL, hemoglobin 7.2 g/dL and platelet count 261×10^4/μL. The serum biochemical parameters were: albumin 3.5 g/dL, blood urea nitrogen 42 mg/dL, creatinine 2.1 mg/dL, and the estimated glomerular filtration rate was 18 mL/min/1.73 m². Immunological workup results were: immunoglobulin (Ig) G 336 mg/dL (normal: 872-1,825 mg/dL), IgA 41 mg/dL (normal: 95-405 mg/dL) and IgM 12 mg/dL (normal: 59-269 mg/dL). The patient tested negative for antinuclear antibody, rheumatoid factor, myeloperoxidase anti-neutrophil cytoplasmic antibody, proteinase 3 anti-neutrophil cytoplasmic antibody and anti-glomerular basement membrane antibody. The results of the dipstick urine tests were 4+ for proteinuria and 3+ for microscopic hematuria, and the 24-hour urinary protein excretion was 5.8 g/day. An examination of urinary sediment revealed: red blood cells 10-20 cells/high power field (HPF), white blood cells 5-10 cells/HPF and granular casts 1-4/HPF. Ultrasonography of the kidney revealed 12.4% plasma cells. Flow cytometry revealed that the aspirate consisted of 3.1% monoclonal plasma cells with kappa light chains that were Bence-Jones protein (kappa type). Serum free kappa light chains were 21,500 mg/L (normal: 3.3-19.4 mg/L) and lambda light chains were <0.6 mg/L (normal: 0.6-19.4 mg/L), the kappa/lambda ratio was 3,829 (normal: 0.26-1.65). A fluorescence in situ hybridization analysis showed neither t(4;14) and t(14;16), nor del(1p) and CD38+ and CD138+. Immunohistochemical studies showed kappa light chain-positive staining along the glomerular capillary and tubular basement membranes (Fig. 1C, D). Electron microscopy showed diffuse deposition of dense materials along the endothelial side of the basement membrane (Fig. 1E, F). Thus, LCDD was histologically confirmed.

Chemotherapy with bortezomib (1.3 mg/m²), cyclophosphamide (300 mg/m²) and dexamethasone (20 mg/kg body weight) (VCD) was administered. On the next day, laboratory tests showed elevated serum levels of aspartate aminotransferase (219 U/L; normal: 13-30 U/L), alanine aminotransferase (250 U/L; normal: 7-23 U/L), alkaline phosphatase (ALP) (1,152 U/L; normal: 106-322 U/L), and γ-glutamyl transpeptidase (γ-GTP) (331 U/L; normal: 9-32 U/L). Ultrasound imaging of the liver revealed no evidence of hepatomegaly, splenomegaly or ascites. Serological tests for hepatitis B and C viruses, Epstein-Barr virus and cytomegalovirus were all negative. Subsequent chemotherapy was discontinued. However, serum levels of hepatobiliary enzymes increased further (ALP 2,025 U/L and γ-GTP 445 U/L). To determine the cause of liver dysfunction, a percutaneous liver biopsy was performed. Hematoyxlin and Eosin and Masson trichrome staining of the prepared tissue sections showed thickened peri-cellular Disse spaces (Fig. 2A). Immunohistochemical studies showed kappa light chain deposition (Fig. 2B), which is compatible with LCDD. Glycyrrettinic acid was administered and serum levels of hepatobiliary enzymes gradually decreased. Thereafter, the chemotherapy regimen was repeated with a weekly administration of subcutaneous bortezomib 1.3 mg/m² and dexamethasone (BD) 20 mg/kg body weight was restarted.

During the second cycle of BD chemotherapy, laboratory tests showed an elevation of thyroid-stimulating hormone 43.08 μU/L (normal: 0.27-4.2 μU/L) and decreased free thyroxine 0.86 pg/ml (normal: 1.0-1.8 pg/ml). Thyroid ultrasound imaging revealed no abnormalities and tests for anti-thyroglobulin antibody and anti-thyroid peroxidase antibody were negative. Although a thyroid gland biopsy was not performed, hypothyroidism associated with LCDD was suspected and levothyroxine treatment was initiated. The patient also complained of visual impairment. Optical coherence tomography showed protuberances on the retinal pigment epithelial layer (Fig. 2C). Levels of free kappa light chains in the anterior aqueous humor were 27.3 mg/L (normal: 3.3-19.4 mg/L) and lambda light chains were <0.6 mg/L (normal: 0.26-1.25 mg/L), suggesting ocular involvement in LCDD. Moreover, the patient developed dyspnea and bilateral leg edema. The electrocardiogram showed no detrimental changes. However, chest radiography revealed pulmonary edema. Echocardiography showed left ventricular wall thickening, pericardial effusion and a granular sparkling pattern indicative of amyloid cardiac disease (Fig. 3). Cardiac involvement related to LCDD was highly suspected, and furosemide was started for volume overload. After two cycles of BD therapy, the serum kappa/lambda ratio was elevated to 5,785 and serum creatinine increased to 3.80 mg/dL. To intensify the therapy, subcutaneous bortezomib (1.3 mg/m² on days 1, 8, 15) was combined with melphalan (5.6 mg/m² on days 1-4) and prednisone (40 mg on days 1-4). After two
cycles, the intervals of VMP therapy were reduced as follows: melphalan (5.6 mg/m² on days 1-4) and prednisone (40 mg on days 1-4) every six weeks combined with bi-weekly bortezomib (1.3 mg/m²). The clinical course is shown in Fig. 4. After two years, serum free kappa light chain levels decreased to 1,510 mg/L (>90% reduction from the baseline, indicating a very good partial response) and serum creatinine decreased to 1.9 mg/dL. The patient exhibited no clinical symptoms, such as dyspnea, edema, arrhythmia or visual impairment.

**Discussion**

We herein describe a patient with LCDD who developed renal failure, liver dysfunction, hypothyroidism, visual impairment and congestive heart failure. The VCD regimen was associated with liver toxicity, while BD therapy was ineffective. In contrast, VMP therapy for two consecutive years with a reduced dose intensity compared with that used for regular cycles significantly decreased serum free kappa light chain levels and improved renal function without any obvious adverse effects.

The incidence of LCDD is reported to be 0.33% of all kidney biopsies in patients aged over 18 years (5). The disease often develops in the fifth and sixth decades of life and one third of cases also occur in patients aged under 50 years (6). In general, the prognosis of LCDD is poor and most LCDD patients with renal involvement eventually develop end-stage renal disease (ESRD) despite aggressive treatment (5). The median survival time is approximately
four years. The median duration from the diagnosis of LCDD to ESRD is reported to be 2.7 years and renal survival is 54% at 2 years (7). Risk factors for mortality are age at diagnosis, LCDD caused by multiple myeloma and extra-renal light chain deposition (7). Our patient fulfilled some of these factors (older age, and liver, heart, retina and thyroid involvement). Reports of multiple organ damage due to LCDD, as in the present case, are quite rare, and the prognosis seems to be poor. One previous report described a 56-year-old man diagnosed with LCDD with renal, cardiac, liver and neurological dysfunction, who died two months after diagnosis despite cyclophosphamide and prednisone therapy (8).

Various treatment regimens have been used for LCDD to suppress the light chain production and manage existing organ dysfunction. Melphalan combined with prednisone has been used for LCDD with or without multiple myeloma but the response is limited (2). Some case reports showed that

**Figure 2.** Histology of a liver biopsy and optical coherence tomography. (A) A liver section showing thickened peri-cellular Disse spaces (arrows). Hematoxylin and Eosin staining, original magnification: ×200, scale bar: 100 μm. (B) Immunohistochemical staining for kappa light chain revealing positive deposition in the Disse spaces. Original magnification: ×200, scale bar: 100 μm. (C) Optical coherence tomography showing protuberances on the retinal pigment epithelial layer (arrows).

**Figure 3.** Echocardiography imaging. (A) Left ventricular wall thickening (small arrow) and pericardial effusion (large arrow) are evident. (B) A granular sparkling pattern indicating cardiac light chain deposition (arrow).
Bortezomib is a modified dipeptidyl boronic acid and reversible 26S inhibitor, which inhibits the nuclear factor-kappa B signaling pathway and decreases transforming growth factor-β expression (12). In previous studies, bortezomib was administered safely to multiple myeloma patients with renal failure, including those undergoing dialysis (13). Similar results have been reported among LCDD patients. Table shows a list of previous reports describing patients with LCDD who received bortezomib-based regimens without high-dose chemotherapy (11, 14, 15). The patient described here showed an abrupt elevation in the serum levels of hepatobiliary enzymes after the first cycle of the VCD regimen. Although the liver is one of the most frequent extra-renal sites of LCDD involvement (3), chemotherapy-induced liver damage is also considered, although this is un-

Table. Reported Cases with LCDD Treated with Bortezomib-based Regimens.

<table>
<thead>
<tr>
<th>Ref No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Type of light chain</th>
<th>MM</th>
<th>Serum Cr before treatment (mg/dL)</th>
<th>Treatment regimen</th>
<th>Hematological response</th>
<th>Serum Cr after treatment (mg/dL)</th>
<th>Follow-up period (months)</th>
</tr>
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<tr>
<td>11</td>
<td>56</td>
<td>Male</td>
<td>Kappa –</td>
<td>1.9</td>
<td>Bortezomib/cyclophosphamide/dexamethasone</td>
<td>PR</td>
<td>1.1</td>
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<td>Male</td>
<td>Kappa +</td>
<td>5.0</td>
<td>Bortezomib/cyclophosphamide/dexamethasone</td>
<td>PR</td>
<td>2.6</td>
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<td></td>
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<tr>
<td>11</td>
<td>33</td>
<td>Male</td>
<td>Lambda –</td>
<td>1.9</td>
<td>Bortezomib/cyclophosphamide/dexamethasone</td>
<td>PR</td>
<td>1.1</td>
<td>12</td>
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<tr>
<td>14</td>
<td>58</td>
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<td>Kappa +</td>
<td>8.2</td>
<td>Bortezomib/doxorubicin/dexamethasone</td>
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<tr>
<td>15</td>
<td>56</td>
<td>Female</td>
<td>Kappa –</td>
<td>3.6</td>
<td>Bortezomib/dexamethasone</td>
<td>PR</td>
<td>1.7</td>
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<tr>
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<td>46</td>
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<td>Kappa –</td>
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<td>CR</td>
<td>1.8</td>
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<td>CR</td>
<td>2.4</td>
<td>12</td>
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<tr>
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<td>67</td>
<td>Male</td>
<td>Lambda –</td>
<td>2.4</td>
<td>Bortezomib/dexamethasone</td>
<td>PR</td>
<td>1.7</td>
<td>N/A</td>
<td></td>
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<tr>
<td>Our case</td>
<td>70</td>
<td>Female</td>
<td>Kappa –</td>
<td>2.1</td>
<td>Bortezomib/melphalan/prednisone</td>
<td>VGPR</td>
<td>1.9</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Cr: creatinine, CR: complete remission, LCDD: light chain deposition disease, MM: multiple myeloma, N/A: not applicable, PR: partial remission, Ref: reference, VGPR: very good partial remission

treatment with high-dose melphalan followed by autologous stem cell transplantation led to a hematological response (9) and improvement of renal function (10). However, high-dose chemotherapy is sometimes toxic and fatal (10). The patients’ age and extra-renal manifestations, especially cardiac involvement, are associated with complications and death after autologous stem cell transplantation (3). Another report showed that intensive chemotherapy was more toxic in patients with LCDD compared with those with multiple myeloma (11). Thus, patients should be carefully assessed before such aggressive treatment is administered.

Bortezomib is a modified dipeptidyl boronic acid and reversible 26S inhibitor, which inhibits the nuclear factor-kappa B signaling pathway and decreases transforming growth factor-β expression (12). In previous studies, bortezomib was administered safely to multiple myeloma patients with renal failure, including those undergoing dialysis (13). Similar results have been reported among LCDD patients. Table shows a list of previous reports describing patients with LCDD who received bortezomib-based regimens without high-dose chemotherapy (11, 14, 15). The patient described here showed an abrupt elevation in the serum levels of hepatobiliary enzymes after the first cycle of the VCD regimen. Although the liver is one of the most frequent extra-renal sites of LCDD involvement (3), chemotherapy-induced liver damage is also considered, although this is un-
common in LCDD patients. However, two cases have been reported with severe and fatal hepatic failure after vincristine, doxorubicin and dexamethasone (VAD) therapy (16, 17). Considering the patient’s frailty as well as the multiple organ involvement of LCDD in the present case, we concluded that neither high-dose chemotherapy with autologous stem cell transplantation nor the VCD regimen were appropriate. Elderly patients with LCDD should be treated with a milder regimen.

VMP therapy is recognized as standard for patients with multiple myeloma who are ineligible for high-dose chemotherapy (18). This therapy has also been shown to be superior to conventional melphalan and prednisone therapy. In preclinical studies, bortezomib sensitized both melphalan-sensitive and melphalan-resistant myeloma cell lines to melphalan, downregulated cellular responses to genotoxic stress and restored sensitivity to melphalan-resistant myeloma cell lines (19). Although LCDD treated by VMP therapy has not been reported to date, this current case suggests that the efficacy of VMP therapy for LCDD is similar to that for multiple myeloma.

A longer period of treatment may be required for the improvement of organ function affected by LCDD, because clearance of the light chains deposited in the involved organs is not rapid. In the present case, the interval of bortezomib chemotherapy was reduced to bi-weekly, resulting in a reduction in the relative dose intensity. Compared with the VMP regimen (comprising five to nine cycles) in the VISTA trial (18), the relative dose intensity was reduced to 75% for bortezomib, 63% for melphalan and 50% for prednisolone. It can be speculated that VMP therapy at this reduced dose intensity will allow the patient to be administered bortezomib for a longer period without serious adverse effects. The clinical importance of our case is based on the potential to treat frail patients with a higher degree of light chain deposition in multiple organs with a milder chemotherapy regimen for a longer period, rather than with highly intensive chemotherapy, such as the VCD regimen.

In summary, we herein described a patient who developed LCDD with multiple organ involvement. The patient was successfully treated with long-term VMP therapy with a reduced dose intensity. This report emphasizes that patients with LCDD who are elderly or affected by extra-renal organ involvement should be treated with mild chemotherapy regimens with a relatively low dose intensity for a prolonged period.

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

References