Successful Bortezomib/dexamethasone Induction Therapy with Lenalidomide in an Elderly Patient with Primary Plasma Cell Leukemia Complicated by Renal Failure and Pulmonary Hypertension

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Abstract

Primary plasma cell leukemia (PPCL) is a rare disease that progresses rapidly. In such cases, it is difficult to achieve remission, and early intensive chemotherapy is recommended. We herein describe the case of a 76-year-old man with PPCL complicated by renal failure and pulmonary hypertension. Bortezomib/dexamethasone induction therapy with lenalidomide was administered in association with continuous hemodiafiltration (CHDF). Complete remission was achieved after a single course of treatment, resulting in the cessation of CHDF. With the patient in remission, the administration of beraprost and bosentan resulted in improvements in the pulmonary hypertension. The results of this case report support the use of bortezomib/lenalidomide/dexamethasone combination therapy as an effective treatment for elderly PPCL patients with various complications.

Key words: primary plasma cell leukemia, renal failure, pulmonary hypertension, bortezomib, lenalidomide

(Intern Med 53: 1171-1175, 2014)
(DOI: 10.2169/internalmedicine.53.1672)

Introduction

Primary plasma cell leukemia (PPCL) is characterized by the presence of >20% and/or an absolute number of more than 2,000/μL plasma cells in the peripheral blood, with no history of multiple myeloma (MM) (1, 2). PPCL is a rare variant of MM and accounts for only 1-4% of all myelomas. PPCL progresses more rapidly than other myelomas, and achieving complete remission (CR) is difficult, as the prognosis of PPCL patients receiving standard chemotherapy is very poor, with a median survival time (MST) of only seven months (1, 2). Although early intensive treatment with bortezomib and/or immunomodulatory drugs (IMiDs) is recommended in PPCL patients, few studies have investigated appropriate chemotherapy regimens due to the rarity of PPCL (1-4). Autologous and/or allogeneic stem cell transplantation (SCT) may serve as a more effective therapeutic option in eligible PPCL patients with a favorable performance status (PS) (1, 2). We herein report the case of an elderly PPCL patient with renal failure (RF) and pulmonary hypertension (PH). The patient’s severe complications were successfully treated while achieving CR with a single course of bortezomib/dexamethasone (BD) induction therapy with lenalidomide.

Case Report

A 76-year-old man was admitted to a community hospital one year ago for bacterial pneumonia and chronic heart failure (CHF). He received intensive care unit (ICU) management, and his clinical findings improved over two months. One year after discharge, he was transferred to the emergency department at our hospital by ambulance with fatigue,
Figure 1. Microscopic findings of Giemsa staining of the peripheral blood (A). The complex karyotype observed on the G-banding chromosomal examination of the same sample (B).

Figure 2. Chest X-ray (A) and CT (B) examinations performed on admission to our hospital. A chest X-ray and CT revealed an enlarged heart with bilateral pleural effusion.

Leg edema and dyspnea on exertion (Medical Research Council dyspnea scale grade 3) lasting for one week. We suspected an exacerbation of CHF, and the patient was admitted to our hospital for further examinations. A physical examination performed on admission revealed hypotension (dopamine 5γ) and hypoxia (oxygen saturation: 94% on nasal oxygen at 3 L/min) with a slight fever. The patient presented with conjunctival anemia, jugular venous distention, a cardiac murmur, wheezing and edema in both lower limbs in addition to oliguria. Laboratory examinations revealed significantly abnormal findings, including a white blood cell (WBC) count of 18,500/μL with 65% plasma cells (Fig. 1A), a hemoglobin level of 9.5 g/dL, a platelet count of 6.5×10^4/μL, a creatinine (Cr) level of 2.66 mg/dL and a blood urea nitrogen (BUN) level of 85.5 mg/dL. An increase in the IgA monoclonal component serum level (2,049 mg/dL) was noted, and the serum free light chain (FLC) κ/λ ratio was 822.22. The deletion of the long arm on chromosome 13 (del13q) was identified on interphase fluorescence in situ hybridization (FISH) in the peripheral blood; however, no chromosomal translocations, including t(11;14), t(4;14) and t(14;16), or deletion of the short arm on chromosome 17 were detected. An examination of chromosomes using G-Banding revealed the complex karyotype, including del13q, and abnormalities in immunoglobin heavy chains (IgHs) were found in four of the seven cells (Fig. 1B). On admission, a chest X-ray and simple computed tomography showed an enlarged heart with bilateral pleural effusion, although no extramedullary masses were noted (Fig. 2).

The patient was diagnosed with PPCL soon after admission and entered the ICU. His PS was four. We selected intensive chemotherapy because PPCL is an aggressive disease with a poor prognosis (5). BD induction therapy with bortezomib (1.3 mg/m² administered subcutaneously on days 1, 4, 8 and 11) and dexamethasone (20 mg/day administered orally on days 1, 2, 4, 5, 8, 9, 11 and 12) was started on the
same day. Echocardiography demonstrated a normal left ventricle function (ejection fraction: 82%), although the estimated mean pulmonary artery pressure (mPAP) was high at 59 mmHg (<25 mmHg) (6). The patient was unable to undergo right heart catheterization due to his poor general condition. We simultaneously introduced continuous hemodiafiltration (CHDF) in combination with chemotherapy. The plasma cell count in the peripheral blood continued to increase following the initiation of treatment. Laboratory examinations performed on the fourth day of hospitalization revealed a WBC count of 30,000/μL (with 73% plasma cells). We therefore initiated treatment with lenalidomide at a dose of 10 mg/day on the same day in addition to the BD induction therapy. The proportion of plasma cells in the peripheral blood began to markedly decrease the following day (Fig. 3). The circulating plasma cells disappeared on the eighth day after the addition of lenalidomide, and the patient’s laboratory data improved. He eventually became free of catecholamines, resulting in the cessation of CHDF, and was discharged from the ICU 10 days after admission. The serum levels of Cr and BUN were maintained within the normal ranges after discharge.

Unfortunately, the patient developed serious respiratory failure on the 14th day of hospitalization. Echocardiography revealed an estimated mPAP of 69 mmHg with massive bilateral pleural effusion, indicating exacerbation of the CHF. Tolvaptan was administered concomitantly with furosemide, and the lenalidomide was subsequently withdrawn. The patient’s respiratory failure gradually improved following the oral administration of these drugs. On the 24th day, he developed methicillin-resistant Staphylococcus aureus (MRSA) pneumonia, and linezolid (1,200 mg/day) was administered orally for one week. Although the CHF and MRSA pneumonia were controlled, the PH did not improve (estimated mPAP: 58 mmHg). The serum IgA level was around the normal range during this time (Fig. 3). We introduced treatment with beraprost and bosentan for PH after achieving control of the disease. Stringent CR (serum IgA: 182 mg/dL, serum FLC κ/λ ratio: 1.46) was obtained on the 70th day of hospitalization. The patient’s PH also improved without bilateral pleural effusion (estimated mPAP: 48 mmHg), and he was able to walk with assistance before being discharged. Because he lived far from the hospital, it was difficult for him to regularly visit our hospital after discharge. Although a single course of lenalidomide (15 mg/day, days 1-21) plus dexamethasone (10 mg/day, days 1, 8, 15, 22) was administered as consolidation therapy on admission, the patient developed grade 3 hematological abnormalities, including thrombocytopenia and anemia. He was subsequently treated with maintenance therapy consisting of low-dose lenalidomide (5 mg/day, days 1-21) and dexamethasone (8 mg/day, days 1, 8, 15, 22) without serious adverse effects at our outpatient department. He remained in remission eight months after diagnosis.

Discussion

PPCL, a rare variant of MM that progresses rapidly with a poor prognosis, has only been described in case reports and retrospective studies. Therefore, no therapeutic strategy for PPCL has so far been established in daily clinical practice. Previous studies have demonstrated that combination therapy with vincristine, doxorubicin and dexamethasone (VAD) or VAD-like regimens is associated with poor results, with an overall response rate (ORR) of 45% and an MST of seven months (7-10). Retrospective studies of combination therapy including bortezomib as a first-line treatment for PPCL have reported ORRs of 80-90% and overall survival (OS) rates at 21 months of 50-60%, which reflect better outcomes than those of previous regimens (3, 4). The poor
prognosis of PPCL is associated with high mortality a few months after diagnosis due to rapid disease progression and/or the development of severe complications (2). Therefore, providing treatment for early tumor reduction is recommended in PPCL patients in order to improve the prognosis (4). In the present case, numerous plasma cells continued to be detected in the patient’s peripheral blood four days after the initiation of BD induction therapy; therefore, we administered an additional drug with the combination therapy in order to achieve further reductions.

Various combination therapies for newly diagnosed MM have been reported in prospective clinical trials targeting transplant-eligible or -ineligible patients (11, 12). Combination therapy including bortezomib and IMiDs has been shown to achieve better outcomes. As bortezomib/lenalidomide/dexamethasone (VRD) therapy for newly diagnosed MM has an ORR of 100% and a progression-free survival rate of 75% at 18 months, it is considered to be one of the most effective combination therapies currently available (13). Combination therapy with lenalidomide and dexamethasone is used as salvage chemotherapy for recurrent or refractory PPCL and has been shown to achieve relatively good outcomes (14, 15). Three patients with PPCL receiving VRD therapy were recently reported, all form of case reports (16, 17). All three patients exhibited a favorable clinical course without any adverse events. The present patient was an elderly patient with severe complications, including RF and PH. We combined BD induction therapy with lenalidomide due to their expected synergistic effects. As a result, stringent CR was achieved after a single course of combination therapy. Treatment for some complications and sufficient rehabilitation were carried out while the patient was in remission. Future prospective studies are needed to evaluate the effects of VRD therapy in transplant-ineligible PPCL patients.

Patients with POEMS syndrome, a rare plasma cell disease, are known to be at high risk of developing PH (18). PH has also been reported to be a rare complication of MM. PH complicated with MM can be associated with amyloid deposition in the pulmonary arteries (19, 20); however, the cause of this phenomenon remains unclear. The present patient’s PH did not progress after he achieved stringent CR. This outcome suggests a possible association between MM and PH. In addition, Lafaras et al. reported that some MM patients receiving thalidomide develop non-thromboembolic PH (21). Therefore, lenalidomide, not thalidomide, was chosen as the third drug in the combination therapy used in this case, in which the patient had severe PH. Although this side effect has not occurred in the present patient since the administration of lenalidomide, continued careful follow-up is needed.

One of the primary complications of MM is RF. Based on pharmacokinetics, the administered doses of bortezomib and thalidomide do not need to be markedly reduced even if the patient has RF. Lenalidomide, which is excreted by the kidneys, requires dosage adjustment in order to obtain an acceptable creatinine clearance value (22). The incidence of adverse effects of lenalidomide has been shown to be significantly higher, in association with severe hematological toxicities, in MM patients with severe RF than in patients with moderate or mild RF (23). The dose of lenalidomide is generally reduced to 5 mg daily in MM patients receiving dialysis. Since the present patient had severe RF, he underwent CHDF on admission. However, no recommended dosage of lenalidomide has been established for patients undergoing CHDF (24). The oral administration of 10 mg/day of lenalidomide was effective for treating the PPCL in this case. Although the CHF was exacerbated due to the withdrawal of CHDF, no severe hematological toxicities were observed during the administration of lenalidomide. The accumulation of more case reports is required in order to determine the appropriate dosage of lenalidomide for myeloma patients undergoing CHDF.

In a retrospective study of PPCL by Pagano et al., the multivariate analysis revealed no significant differences in OS between the group administered bortezomib and/or thalidomide and the group treated without either drug (25). Significant differences in OS have only been observed in PPCL patients with a history of autologous or allogeneic SCT. Another reason for the poor prognosis of PPCL is the short remission period before recurrence. Therefore, the development of novel therapies to maintain long-term remission is needed (2). The present patient was not eligible for SCT. After receiving a single course of consolidation therapy, he is currently being treated with maintenance therapy with low-dose lenalidomide in order to maintain low-term remission. Investigations of consolidation and maintenance therapy for transplant-ineligible PPCL patients are also of importance in order to establish factors affecting long-term survival.

The present results suggest that VRD induction therapy is an effective option in elderly PPCL patients who are not eligible for SCT. The present patient was successfully treated for various complications under stringent CR using combination therapy. However, it is necessary to further evaluate the efficacy and toxicity of VRD induction therapy in elderly PPCL patients.

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

References


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