Improvement of Cardiac Diastolic Function and Prognosis After Autologous Peripheral Blood Stem Cell Transplantation in AL Cardiac Amyloidosis

Shusuke Yagi¹, Masashi Akaike¹, Shuji Ozaki¹, Chikako Moriya¹, Kyoko Takeuchi¹, Tomoko Hara¹, Mitsunori Fujimura¹, Yuka Sumitomo¹, Takashi Iwase¹, Yasumasa Ikeda¹, Ken-ichi Aihara¹, Takehiko Kimura², Takeshi Nishiuchi², Masahiro Abe¹ and Toshio Matsumoto¹

Abstract

AL amyloidosis is a disease in which immunoglobulin L chain is deposited in multiple organs, and the prognosis of cardiac amyloidosis is extremely poor. Although several treatments based on that for multiple myeloma, have been performed, there is no clear evidence that cardiac function is improved. We report a case of AL cardiac amyloidosis with moderate cardiac dysfunction for which we performed autologous peripheral blood stem cell transplantation (auto-PBSCT) in combination with high-dose melphalan therapy. This treatment resulted in significant improvement in cardiac function and good prognosis for about 3.5 years after the diagnosis. Therefore, auto-PBSCT is a possible option as up-front therapy for AL cardiac amyloidosis.

Key words: AL cardiac amyloidosis, autologous peripheral blood stem cell transplantation, prognosis, cardiac diastolic function

DOI: 10.2169/internalmedicine.46.0142

Introduction

Immunoglobulin light chain-associated (AL) amyloidosis is a disease that presents several clinical symptoms due to amyloid deposition in systemic organs such as the heart, liver, kidney, tongue, gastrointestinal tract, skin, and peripheral nerves (1). Amyloid is a peculiar form of an insoluble fibrillar protein with a beta-pleated-sheet configuration, and amyloid fibrils trigger irreversible impairment of organ function. Cardiac amyloidosis has a poor prognosis, and the mean prognosis has been reported to be 6 months or after the onset of symptoms of heart failure (2-4). The amyloidogenic protein is an immunoglobulin light chain or a fragment of a light chain that is produced by a clonal population of plasma cells in bone marrow. Several treatments for AL amyloidosis based on treatment for multiple myeloma have been performed. These treatments include MP (melphalan and prednisolone) therapy (5-7), VAD (vincristine, doxorubicin, and dexamethasone) therapy (8), interferon therapy (9), and high-dose dexamethasone therapy (10). However, such treatments have not resulted in sufficient improvement of cardiac function and prognosis. We report a case of AL cardiac amyloidosis in which we performed autologous peripheral blood stem cell transplantation (auto-PBSCT) in combination with high-dose melphalan therapy. This treatment resulted in significant improvement in cardiac function and good prognosis for about 3.5 years after the diagnosis.

Case Report

A 63-year-old woman visited a hospital because of palpitation in 2002. A 12-lead electrocardiography (ECG) revealed first-degree atrioventricular block and low voltage in the limb lead. Multifocal premature ventricular contractions were observed on a 24-h Holter ECG. An echocardiographic
image revealed left ventricular hypertrophy with granular sparkling. Cardiac amyloidosis was suspected from the ECG and echocardiography findings. She was referred to our hospital for further examination and treatment on October 21, 2003. Her height and weight were 142 cm and 39 kg, respectively. Blood pressure was 110/68 mmHg and heart rate was 88/min. There was no cardiac murmur, but fourth heart sounds were heard. ECG showed a QS pattern in leads V1-3, a strained ST depression in V5-6, and low voltage in the limb lead (Fig. 1). Echocardiography findings revealed thickening of 14 mm in both the ventricular septal and posterior walls and diffuse thickening of the left ventricle. However, the left ventricular end-diastolic diameter remained at 38 mm with no expansion and 65% of the left ventricular ejection fraction was also preserved (Fig. 2A, B).

In the parasternal long axis view, there was increased luminae and a granular sparkling pattern in the ventricular septum. The E/A ratio of the left ventricular transmitral inflow had increased to 2.1 and deceleration time had shortened to 110 msec. In addition, D-wave progression was noted in the pulmonary vein inflow, indicating impaired left ventricular diastolic function (Fig. 3A). In a $^{99}$mTc-PYP scintigram, there was accumulation from the anterior wall to the cardiac apex, suggesting myocardial damage at the same site (Fig. 4A).

Blood test findings revealed mild normocytic anemia and a mild increase in monoclonal $\gamma$-globulin in a serum proteinogram (Fig. 5A). Serum IgA level was 163 mg/dL and IgA monoclonal protein was detected by serum immuno-electrophoresis. A bone marrow smear showed a normocellular pattern with 3.2% plasma cells. These findings ruled out a diagnosis of multiple myeloma. Since AL amyloidosis was suspected from the above findings, gastric mucosa biopsy was performed to confirm the diagnosis. Hematoxylin and eosin staining showed amorphous eosinophilic materials in the vascular wall of the gastric mucosa, and amyloid deposition was confirmed by Congo-red staining with or without permanganate treatment (Fig. 6A, B). Therefore, the patient was clinically diagnosed with AL cardiac amyloidosis based on the findings of ECG, echocardiography and $^{99}$mTc-PYP scintigram. It was thought that the prognosis of this patient with severe cardiac diastolic dysfunction due to AL cardiac amyloidosis would be poor with conventional therapies, and autologous peripheral blood stem cell transplantation (auto-PBSCT) with high-dose chemotherapy was therefore performed to eradicate plasma cells that produce amyloidogenic immunoglobulin light chains. The protocol used for the patient was in accordance with the guidelines provided by the Ethical Review Committee of Tokushima

Figure 1. Twelve-lead electrocardiogram on admission. An ECG revealed first-degree atrioventricular block and low voltage in the limb lead.

Figure 2. Echocardiographic findings on admission. A: B-mode echocardiographic image revealed left ventricular hypertrophy with granular sparkling. B: M-mode echocardiographic image showed that cardiac contraction was preserved.
University Hospital. Informed consent was obtained from the patient before treatment. The cardiac function of the patient was judged capable of enduring high-dose chemotherapy, and auto-PBSCT was planned as first-line treatment.

Peripheral blood stem cells were mobilized by etoposide (240 mg, for 3 days) and granulocyte colony-stimulating factor (50 μg/m²/day), and CD-34 positive cells (10.9x10⁶/kg) were collected. High-dose melphalan therapy (120 mg, for 2 days) was performed on February 15 followed by a transplant on February 18th. These procedures were carefully monitored by vital signs and ECG. Hematological recovery was observed on day 10 without complications due to bone marrow suppression or associated with high-dose melphalan therapy. After the transplant, the small amount of M protein was completely eliminated (Fig. 5B).

Echocardiography examination one month later showed that the E/A ratio of the left ventricular mitral inflow pattern and D-wave height of the pulmonary vein inflow were decreased, indicating improvement in diastolic dysfunction (Fig. 3B). End-diastolic dimension and wall thickness, a parameter of cardiac morphology, and fractional shortening, a parameter of systolic function, were not changed. A ⁹⁹mTc-PYP scintillogram at 4 months after transplantation showed that the accumulation from the anterior wall to the cardiac apex was decreased (Fig. 4B). Although the patient had no history of heart failure and no symptoms or signs suggestive of congestive heart failure during or after chemotherapy, only a low-dose of candesartan (4 mg) was prescribed with the expectation of cardiac protection. Although the brain natriuretic peptide (BNP) level was 128 pg/mL before the transplantation, it was decreased to 56 pg/mL at 8 months after the transplantation and has been maintained at about 50 pg/mL for 3.5 years. The patient is still making outpatient visits with no decrease in quality of life and no elevation of BNP level for about 3.5 years since the diagnosis.

**Discussion**

The diagnosis of amyloidosis is based on histological findings in specimens from symptomatic organs. However,
Figure 5. Serum proteinogram findings. A: A small amount of M protein was detected before treatment. B: M protein was eliminated after treatment.

Figure 6. Histological findings of gastric mucosa biopsy. A: Hematoxylin and eosin staining showed amorphous eosinophilic materials in the vascular wall of the gastric mucosa. B: These materials were positive for Congo-red staining, which confirmed amyloid deposition.

direct biopsy of an impaired organ is not always feasible. In such a case, it is acceptable to make a diagnosis of amyloidosis if adequate deposition of insoluble fibrillar protein is confirmed in other organs or tissues. In addition, when M protein is detected by electrophoresis of serum and urine, proliferation of monoclonal plasma cells needs to be verified for the differential diagnosis of AL amyloidosis and multiple myeloma. In this patient, characteristic findings of cardiac amyloidosis were observed by echocardiography, and amyloid deposition was confirmed from histological findings of gastric mucosa. Although serum immunoelectrophoresis revealed monoclonal IgAλ protein, proliferation of plasma cells was not detected in the bone marrow. Therefore, we made a diagnosis of AL cardiac amyloidosis.

Cardiac AL amyloidosis has an extremely poor prognosis. Cueto-Garcia et al reported that the occurrence of clinical congestive heart failure was strongly correlated with greater wall thickness and that the median survival of the patients who had 15 mm or greater wall thickness was only 0.4 years (11). It has also been reported that the 1-year probability of survival was 49% in cardiac amyloidosis patients who had a deceleration time of 150 msec or less, as measured by pulsed-wave Doppler of left ventricular inflow. In our patient, the deceleration time was 110 msec, which indicates a poor prognosis (12).

Treatment of AL amyloidosis has been directed towards reducing the production of amyloid precursors from plasma cells. However, removal of amyloid deposits is difficult and the prognosis of amyloidosis remains poor. MP therapy has been performed for the purpose of inhibiting the production of M proteins, but there have been no obvious clinical effects such as improvement in prognosis (5-7). Potent chemotherapies such as VAD therapy (8), interferon therapy (9), and high-dose dexamethasone therapy (10) have also been performed and improvement in clinical symptoms has been reported for some patients, but overall survival has not been extended significantly (13-15).

In recent years, high-dose melphalan followed by auto-PBSCT has been performed for multiple myeloma, and this treatment has significantly prolonged the period of survival (16). Compared with conventional chemotherapies, this approach allows almost complete eradication of plasma cells and is now being used for patients with AL amyloidosis with the expectation of inhibition of the production of the amyloid precursors. However, this disease is usually associated with multiple organ dysfunction such as heart and kidney disorders, which limits the therapeutic application of auto-PBSCT. In fact, there have been several reports of treatment-related death such as death from arrhythmias, sudden death, and death from infection, gastrointestinal hemorrhage and multiple organ failure after auto-PBSCT. Therefore, treatment should be carefully selected for such patients with amyloidosis (17). For application of auto-PBSCT, two sets of criteria have been reported by Mayo Clinic (18) and
Boston University (19) and by the Amyloidosis Research Committee in the Ministry of Health, Labor, and Welfare of Japan (20). According to these reports, the criteria are age \( \leq 65 \) years, M protein in blood or urine, performance status \( \geq 2 \), no clear sign of heart failure, LVEF \( \geq 45\% \) or FS \( \geq 38\% \) by echocardiography, systolic blood pressure \( \geq 90 \) mmHg, oxygen saturation in room air \( \geq 95\% \), serum creatinine \( \leq 2 \) mg/dL, and serum direct bilirubin \( \leq 2 \) mg/dL. These criteria were met in this case, and we performed auto-PBSCT in combination with high-dose chemotherapy for improvement in the cardiac hypertrophy and diastolic function, ultimately for improvement of prognosis.

In this case, auto-PBSCT successfully inhibited the production of M protein without severe treatment-related complications and resulted in improvement of cardiac dysfunction. The left ventricular filling waveform showed improvement from a restrictive pattern to a pseudo-normal pattern. Moreover, a \(^{99m}\text{Tc-PYP} \) scintigram showed decreased amyloid buildup, suggesting improvement of amyloid deposition in the heart. Furthermore, post-treatment BNP level was decreased to almost normal, which is a prognosis predicting improvement in cardiac function. The left ventricular filling waveform showed improvement from a restrictive pattern to a pseudo-normal pattern.

In this case, auto-PBSCT successfully inhibited the production of M protein without severe treatment-related complications and resulted in improvement of cardiac dysfunction. The left ventricular filling waveform showed improvement from a restrictive pattern to a pseudo-normal pattern. Moreover, a \(^{99m}\text{Tc-PYP} \) scintigram showed decreased amyloid buildup, suggesting improvement of amyloid deposition in the heart. Furthermore, post-treatment BNP level was decreased to almost normal, which is a prognosis predicting factor after auto-PBSCT (21). The patient has been making outpatient visits for about 3.5 years since the diagnosis. Although the mechanism by which deposited amyloid disappears is unknown, several studies have shown that the deposition is not irreversible and that there is a possibility of absorbance of amyloid if additional deposition is completely inhibited.

Recent studies have demonstrated that auto-PBSCT significantly improves survival of patients with amyloidosis compared to survival following conventional chemotherapies (12, 19, 22-26). The life expectancy of patients with cardiac amyloidosis who have undergone MP therapy has been reported to be five months, but that has been extended to two years with auto-PBSCT in patients with left ventricular wall thickness of >15 mm. Several medications such as calcium antagonists, digoxin, vasodilators, and beta-blockers are contraindicated (2-4) because many patients are complicated with orthostatic hypotension. Therefore, auto-PBSCT with high-dose chemotherapy is an effective strategy for improving prognosis in cardiac amyloidosis patients whose organ function is preserved. Further clinical studies are needed to elucidate the characteristics of patients for whom this treatment is effective. Although cardiac AL amyloidosis has a poor prognosis, the present case indicates that early diagnosis and treatment are important and that auto-PBSCT is a possible option as up-front therapy in patients with moderate cardiac function.

References


