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ORIGINAL ARTICLE

Combined use of bortezomib, cyclophosphamide, and dexamethasone induces favorable hematological and organ responses in Japanese patients with amyloid light-chain amyloidosis: a single-institution retrospective study

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Abstract Amyloid light-chain amyloidosis (ALA) is a rare disease with poor prognosis and is often associated with monoclonal gammopathy of undetermined significance, multiple myeloma, or Waldenström macroglobulinemia. Only high-dose melphalan with auto-peripheral blood stem cell transplantation (PBSCT) has shown high long-term hematological response rates, but combinations with novel agents, including bortezomib or lenalidomide, have recently shown high hematological response rates for AL amyloidosis patients. In the present study, we treated eight Japanese patients with AL amyloidosis using bortezomib, cyclophosphamide, and dexamethasone (CyBorD). Overall response rate was 100 %; four patients (50 %) had complete remissions (CR), two (25 %) had very good partial responses, and two (25 %) had partial responses. Five of six patients (83 %) had organ responses in the heart and/or kidney. A relapsed patient repeatedly achieved CR with the CyBorD treatment. One patient died of sudden cardiac arrest a month after normalization of his serum free light chain level, which may be attributable to his spending the previous 6 months undergoing PBSCT collection and high-dose melphalan with auto-PBSCT. Altogether, the CyBorD regimen achieved high levels of hematological responses relatively quickly (within 2–3 months). The CyBorD regimen, rather than high-dose melphalan treatment, could serve as a first-line therapy for Japanese patients with ALA.

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Introduction

Amyloid light-chain amyloidosis (ALA) is a rare disease characterized by systemic immunoglobulin light-chain-derived amyloid organ deposits that are produced by plasma cell dyscrasias, including monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM) [1]. Abnormal proliferating plasma cells overproduce light chains, which deposit in almost all organs and become amyloid proteins, leading to organ damage, most frequently affecting the heart, kidney, liver, stomach, intestine, and peripheral nerves. Median overall survival (OS) from diagnosis is about 3 years; however, cardiac complications, such as cardiac hypertrophy, heart failure, and lethal arrhythmias, can shorten median OS to less than 1 year [2]. Renal involvements are also common and can induce refractory nephrotic syndrome, leading to systemic edemas, pleural effusion, and ascites. Most patients finally become hemodialysis dependent. Therefore, they have poor prognoses and need immediate treatment.

Before the novel agent era, to introduce long-term remission of ALA, high-dose melphalan with peripheral blood stem cell transplantation (PBSCT) had been highly effective and improved OS in most patients with ALA [3–5]. However, many patients sometimes have severe organ damage, especially in the heart, and are ineligible for high-dose melphalan therapy [6]. These patients have very poor prognoses. An alternative therapeutic regimen is melphalan and dexamethasone (MD) treatment, but its efficacy is not superior to high-dose melphalan and the MD regimen does not increase survival of patients with advanced-stage (stage

III–IV) disease [7]. Recently, many novel agents have become available for patients with MM, including proteasome inhibitors, bortezomib and carfilzomib, immunomodulatory drugs, thalidomide, lenalidomide, and pomalidomide [8]. Since these drugs can eradicate abnormal plasma cells, they can also be used to kill ALA-producing plasma cells. A combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD) is reported to be highly effective for patients with ALA [9, 10]. Mikhael et al. reported that 12 out of 17 patients achieved complete remission, with an overall response rate of 94 % and less organ damage [9]. A combination of lenalidomide, cyclophosphamide, and dexamethasone was also very active; 6 out of 13 patients achieved at least very good partial remission with an overall response rate of 62 % [9, 11, 12]. These data show that 3-drug combinations with novel agents improved prognosis of patients with ALA.

Recently, a means of assessing free light chain (FLC) has become available, especially for patients with MM. M protein is good marker for tumor burden, but not for ALA, whereas FLC is very powerful tool to evaluate ALA disease status and therapy effectiveness [13]. Therefore, by measuring FLC, we can easily evaluate a regimen's efficacy. We present here our single-center retrospective study of 8 Japanese patients with ALA who were treated with CyBorD.

Methods

Patients

All patients with ALA received CyBorD from May 2010 to Nov. 2013 in our hospital. Serum monoclonal immunoglobulin was detected in all 8 patients. ALA was directly confirmed by biopsies of involved organs, including heart, kidney, and gastrointestinal tracts. Amyloid deposits were histologically determined with the biopsy specimens and were immunologically determined as κ- or λ-type light chains. Before CyBorD therapy, written informed consent was obtained from all of the patients. All the data, including disease profiles, types and serum levels of M proteins, and serum levels of involved free light chain (iFLC) were extracted from medical records. Organ damage was determined with the consensus criteria described in National Comprehensive Cancer Network (NCCN) Guidelines [13], according to which renal involvements were indicated by >0.5 g/day of urine protein and heart involvements by left ventricular wall thickness >12 mm (by echocardiogram), or an elevated N-terminal Pro-B-type natriuretic peptide (NT-ProBNP) >332 ng/L in the absence of renal failure or atrial fibrillation. In our hospital, BNP but not NT-ProBNP is used as an index of heart impairment [14]. Instead of measuring total daily urine protein, we used the urine protein/creatinine ratio [15, 16]. In addition to evaluating the severity of nephrotic syndrome, we used serum albumin levels to reflect reduction of urine protein.

Hematological responses of patients with MM were assessed by the International Myeloma Working Group uniform response criteria [17]. For primary ALA, hematological responses were judged by consensus criteria in the NCCN Guidelines for ALA [13]. Organ responses were judged by the organ response criteria in NCCN Guidelines for AL amyloidosis, according to which a 50 % decrease in 24-h urinary protein excretion without worsened creatinine clearance by 25 % or increased serum creatinine by 0.5 g/dL was considered to be a positive kidney response. Instead, we utilized 50 % decrease in urine/creatinine ratio. Improved cardiac impairment was defined as 2-mm decreased mean interventricular septal thickness, 20 % improvement in ejection fraction, or improvement by the two New York Heart Association classes.

Toxicities were graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

Treatment

The 8 Japanese patients each received 5-week cycles of 1.3 mg/m^2 of bortezomib and 300 mg/m^2 or 200 or 300 mg/body of cyclophosphamide on days 1, 8, 15, and 22, and 8–20 mg of dexamethasone on days 1, 2, 8, 9, 15, 16, 22, and 23. Dependent on risks and adverse events, the dosages of these drugs were reduced, according to the attending physician's judgment. All 8 patients received 200 mg of acyclovir daily for prophylaxis of herpes zoster.

Results

Patient characteristics and treatment

Eight Japanese patients with ALA were treated with a combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD) from 2010 to 2013 (Table 1). They were 5 male patients and 3 female patients, whose mean age was 61.8 years (range 50–76 years). They included four newly diagnosed patients and four patients who were refractory to high-dose melphalan with autologous PBSCT. The median number of regimens before CyBorD therapy was 0.75 (range 0–2 regimens). The median time from the diagnosis to CyBorD therapy was 25.5 months (range 1–73 months). Among the 8 patients, 4 had MGUS, two had asymptomatic MM, and the other two had symptomatic MM (Table 2). All eight patients had M protein at onset, and 2 patient lacked abnormal increase of iFLC (Case 3, 5). Seven patients (87.5 %) were shown to have amyloid

Table 1 Profiles and results of each AL amyloidosis patient receiving CyBorD therapy

Pt	Age (onset)	Sex	κ or λ	Plasma cell dyscrasia	Treatment history	Involved organs	iFLC (mg/L)	M protein (mg/dL)	CyBorD cycles	Hematological response	Organ response	Survival
1	47	F	BJP λ type	MGUS	Auto-SCT	H, K	69.9	BJP	12[a]	CR	H, K	Alive
2	62	M	IgG λ type	MGUS	Auto-SCT	H, K, D	1,260	IgG 1341	3	VGPR	K	Dead
3	49	F	IgG λ type	MGUS	Auto-SCT	K, D	21.4	IgG 551	6	CR	K	Alive
4	61	F	BJP κ type	SMM	Auto-SCT	H, D	378	BJP	2	CR	H	Alive
5	69	M	IgG λ type	MM	Naive	H, D	20.8	IgG 3847	8	CR	H	Alive
6	76	M	IgG κ type	MM	Naive	D	8,900	IgG 2056	12	PR	NA	Alive
7	60	M	BJP λ type	SMM	Naive	D	2,900	BJP	3	PR	NA	Alive
8	66	M	BJP κ type	MGUS	Naive	L, H, D	392	BJP	2	VGPR	NA	Alive

iFLC involved FLC, *D* digestive tract, *L* liver, *H* heart, *K* kidney, *SMM* smoldering multiple myeloma (asymptomatic), *MM* multiple myeloma (symptomatic), *NA* not applicable

[a] 6-cycle CyBorD was performed twice (Fig. 3b)

Table 2 Disease status of multiple myeloma patients

Patient no.	Disease status	Durie Salmon staging	International staging system
4	Asymptomatic MM	I	I
5	Symptomatic MM	I	II
6	Symptomatic MM	II	III
7	Asymptomatic MM	I	I

MM multiple myeloma

deposits in their digestive tracts through endoscopic biopsies; 3 patients (37.5 %) had kidney involvements, all of whom suffered from nephrotic syndrome; and 5 patients (62.5 %) had heart involvements, which resulted in sudden death in 1 patient (Case 2).

All 8 patients successfully received 1.3 mg/m^2 of bortezomib. The targeted doses of cyclophosphamide reached to 106 % because we used doses of 300 mg/day rather than 300 mg/m^2/day for cyclophosphamide due to the frailty of the patients. Dexamethasone doses were sometimes decreased to 8 mg daily because of low performance status or diabetes mellitus.

Efficacy

Eight patients received 2–12 cycles of CyBorD therapy. Hematological responses are summarized in Table 1. Four patients achieved normalized FLC levels (Fig. 1), and 4 patients achieved elimination of M protein (with protein electrophoresis). By Immunofixation electrophoresis of serum and urine, and iFLC, 4 out of 8 patients achieved complete remission (CR). One patient (Case 8) achieved normalized FLC (very good partial response [VGPR]), but was moved to another hospital without confirming CR. Two patients (Cases 6 and 7) failed to achieve normalized iFLC, but their iFLCs were decreased to ~25 and ~33 %, respectively (Fig. 1). Case 6 has been complicated with symptomatic MM, and Case 7 with asymptomatic MM. As bone marrow plasma cells of Case 7 did not reduce to normal levels (from 11.2 to 8.4 %) after CyBorD therapy, Case 7 is now being treated with bortezomib, lenalidomide, cyclophosphamide, and dexamethasone. Case 1, who failed to get a hematological response with high-dose melphalan with auto-PBSCT, received 6 cycles of CyBorD therapy and achieved CR once. Nine months later, her iFLC level had increased to 69.9 mg/L, and she received another 6 cycles of CyBorD therapy and again achieved CR (Fig. 2a). This fact indicates that CyBorD therapy is repeatedly useful and effective for the same ALA patient.

Organ responses are shown in Fig. 3. Of 3 patients with nephrotic syndrome (Cases 1, 2, and 3), 2 were shown by renal biopsies to have renal amyloidosis. All 3 recovered their serum albumin levels and urine protein/creatinine ratios and improved their peripheral edemas (Fig. 3a, b solid lines). Two patients (Cases 1 and 3) did not show increased creatinine levels, whereas the one patient who suffered a sudden death (Case 2) had continuous elevation of creatinine levels (Fig. 3c). Among the 5 patients with heart impairments, 3 (Cases 1, 4, and 5) showed improved BNP levels (Fig. 3d). None of the patients had reduced ejection fraction levels (data not shown).

Myocardial wall thickening was shown by cardiac echogram in Cases 1 and 2 before CyBorD therapy; however, it had not improved after CyBorD therapy.

Survival

Of the 8 patients who received CyBorD therapy, 7 are alive at 10–91 months from onsets (Fig. 4). Case 2 died of cardiac arrest, probably because of lethal arrhythmias. At that time, his iFLC was already normalized by

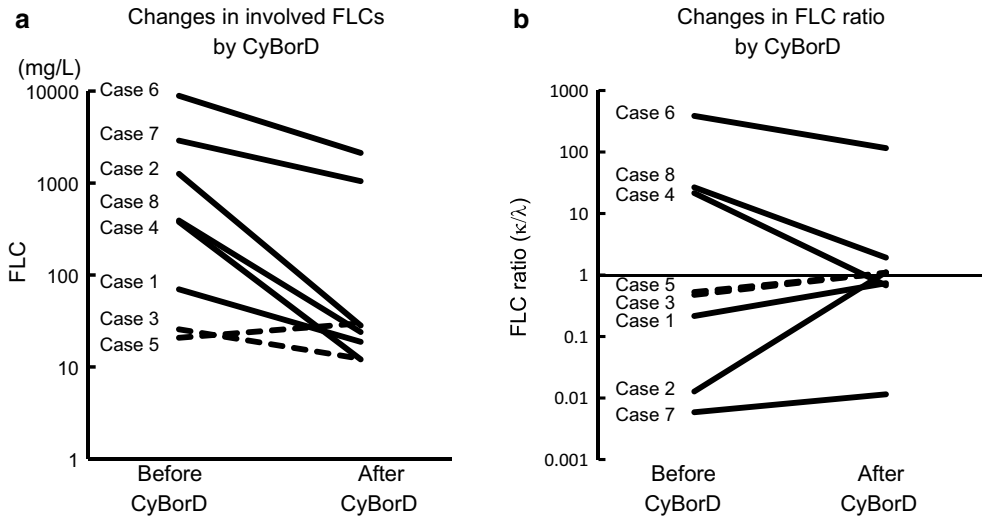

Fig. 1 Involved free light chains (iFLC) were decreased, and κ/λ ratios were normalized by CyBorD therapy. **a** Four patients (Cases 2, 3, 4, and 8) achieved normalized iFLC, and 2 (Cases 6 and 7) had decreased iFLC to ~25 and ~33 %, respectively, of their original levels (*solid lines*). Two patients (Cases 3 and 5) did not have elevation of iFLC (*dashed lines*). **b** Changes in κ/λ ratio were shown. Abnormal κ/λ ratios in 4 of 6 patients were normalized after CyBorD therapy

CyBorD therapy (Fig. 2b), and serum albumin levels had returned to >3.0 mg/dl (Fig. 3a). As he had, at that point, spent 6 months on a regimen of harvested PBSC and high-dose melphalan with auto-PBSCT before CyBorD therapy, high-dose melphalan was not effective for him, he might not have died if he had been treated with CyBorD therapy at first.

Toxicity

Adverse events are summarized in Table 3. All patients had neutropenia, anemia, and thrombocytopenia. However, anemia that required red blood cell transfusion (grade 3) was found in only one patient, although G-CSF or platelet transfusions were not needed. Peripheral neuropathy is a common adverse effect of bortezomib, but only two patients had grade 1 neuropathy because bortezomib was administered weekly. Grades 1 and 2 diarrhea was seen in one and two patients, respectively. Grades 2 and 3 constipation were seen in 1 and 2 patients, respectively. One patient (Case 4) suffered from herpes zoster although she received 200 mg of acyclovir for prophylaxis of herpes zoster. Fever without neutropenia developed in two patients. Interstitial pneumonia of Grade 2 occurred in one patient (Case 8), and was successfully treated by discontinuing CyBorD and administering corticosteroids. One patient (Case 1) suffered from atrial flutter (Grade 3) and successfully treated with intravenous administration of anti-arrhythmic drug. Before the event, she has already been implanted a permanent pacemaker when she suffered from complete AV block. After the event, she has not suffered from atrial flutter and her heart function has been in good condition (cardiac ejection fraction: 62.8 %).

Discussion

We successfully treated 8 Japanese patients with ALA using bortezomib, cyclophosphamide, and dexamethasone (CyBorD) and got good response for all patients, including CR for 4 patients, VGPR for 2 patients, and partial responses for 2 patients. Five patients had organ responses. Renal improvements were especially seen in 3 patients with nephrotic syndrome, including reduced urinary protein, increased serum albumin, and disappearances of edemas. Heart improvements in terms of decreased BNP levels were also seen in 3 out of 5 patients.

Patients with ALA have very poor OS. Until quite recently, a regimen of high-dose melphalan with auto-PBSCT was the standard therapy to achieve remission and improve OS [3–5]. However, many patients with ALA already have severe organ damage, including heart involvement and are therefore ineligible for high-dose melphalan therapy [6]. Among patients who receive high-dose melphalan, around half fail to get good responses and remissions. Several recent reports found 3-drug combinations that included novel agents, such as bortezomib or lenalidomide, were highly effective for patients with ALA [9, 10, 12, 18, 19]. CyBorD is one such treatment regimen, which achieved a high response rate. Mikhael et al. reported that CyBorD achieved CR in 12 and PR

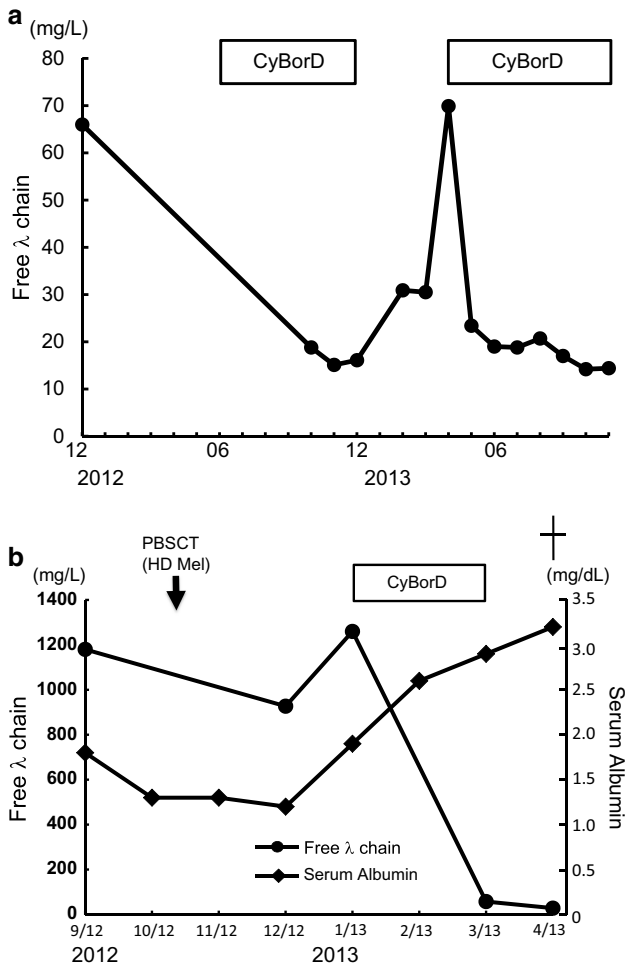

Fig. 2 Clinical courses of patients with ALA. **a** CyBorD was repeatedly effective for the relapsed patient, Case 1. She achieved CR and normalized iFLC after 6 CyBorD cycles. After relapsing with elevated iFLC, she was treated with 6 CyBorD cycles again and achieved normalized iFLC and CR. **b** CyBorD regimen was also highly active for Case 2, who was refractory to high-dose melphalan with auto-PBSCT. He was initially treated with high-dose melphalan with auto-PBSCT, but his iFLC levels did not decrease. He was then treated with CyBorD and achieved normalized iFLC and VGPR, but died of sudden cardiac arrest one month later

in 4 out of 17 patients with ALA, whereas only 1 patient failed to respond [19]. Venner et al. reported that CVD (same as CyBorD) achieved CR in 65 % of newly diagnosed and 21.7 % of relapsed patients with ALA [10]. The lenalidomide, cyclophosphamide, and dexamethasone combination is also reportedly effective, with a response rate of 62 %, including 1 CR and 5 VGPR in 21 patients [12]. Therefore, 3-drug combinations with bortezomib or lenalidomide are very promising therapeutic regimens for patients with ALA, as confirmed by our own findings. In Case 2 in our study, iFLC did not decrease, but instead increased after high-dose melphalan. His iFLC normalized when he was subsequently treated with CyBorD therapy, but he died suddenly soon after. If he had been treated with CyBorD therapy initially, he might have survived much longer. The high response and CR rate (59 %) of CyBorD indicates that it could be a first-line treatment for newly diagnosed Japanese patients with ALA, to replace high-dose melphalan therapy with auto-PBSCT. Early-stage CR is an important goal in managing ALA, to prevent lethal organ damage. However, a prospective large-scale clinical trial of CyBorD for patients with ALA is needed for CyBorD to be considered a first-line treatment.

One patient (Case 1) with severe heart involvement has a pacemaker to prevent cardiac arrest. The patient was refractory to high-dose melphalan but achieved CR with 6 cycles of CyBorD therapy. Six months later, her iFLC rose to its original levels and the patient was again treated with 6 cycles of CyBorD. She achieved a second CR, which implies that CyBorD could be repeatedly effective in the same patients when they suffer from relapses of ALA.

Hematological adverse events from CyBorD therapy are not as severe, only one patient received a red blood cell transfusion and no patients needed G-CSF or platelets transfusions. Peripheral neuropathy was mild; two patients suffered from grade 1 neuropathy. This is because CyBorD is administered once a week, and mainly subcutaneously rather than intravenously [20]. Gastrointestinal adverse events were more severe; 3 patients had Grade 1–2 diarrhea, and 3 had grade 2–3 constipation. Only one patient had grade 3 constipation, which was relieved by reducing his CyBorD regimen from weekly to biweekly. Subcutaneous administration of bortezomib may further reduce toxicity of the CyBorD regimen.

New agents now available to treat MM—a new proteasome inhibitor, carfilzomib, and a new immunomodulatory agent, pomalidomide—might be soon available for patients with ALA [21, 22]. Other agents, including elotuzumab (anti-CS-1 antibody), anti-CD38 antibody, and panobinostat, which are newly available to treat MM might be effective for ALA [23–26].

Prognosis of patients with ALA with MM is reportedly worse than for those with MGUS [27, 28]. In this study, 6 of the patients had at least VGPR, and the other 2 patients had MM which may confirm the previous results. However, the other 2 patients with MM achieved CR. Since these 2 patients with CR did not have serum FLC elevations, but only had serum M protein, patients with ALA without FLC elevations might respond well to CyBorD therapy.

In this single-institution retrospective study, we found that CyBorD in 8 Japanese patients with ALA was effective and relatively safe and achieved 100 % overall response rate (PR or more) with 50 % of CR. Our results indicate that CyBorD is a potential first-line therapy with higher

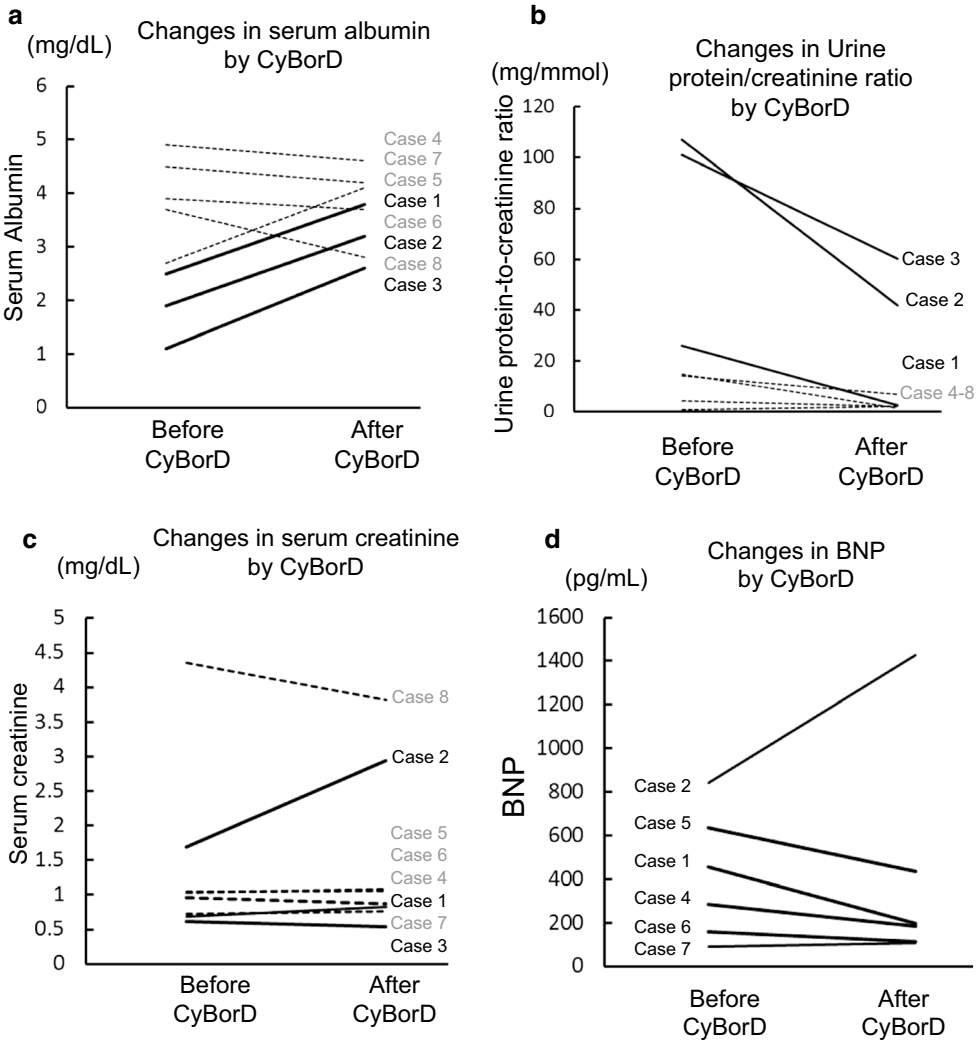

Fig. 3 Organ responses in renal and cardiac impairments by CyBorD therapy. **a** Serum albumin levels recovered to >3.0 g/dl in three patients with nephrotic syndrome (Cases 1, 2, and 3) (*solid lines*). The other patients without nephrotic patients (Cases 4–8) are also shown (*dashed lines*). **b** Urine proteins decreased to normal levels by CyBorD therapy. Instead of measuring daily urine protein levels, we used urine protein/creatinine levels. After CyBorD therapy, urine protein/creatinine levels of Cases 1, 2, and 3 decreased to <50 mg/mmol. **c** Changes in serum creatinine levels before and after CyBorD therapy. **d** BNPs of 3 of 6 patients who had cardiac involvements decreased after CyBorD therapy; BNPs of 2 patients did not increase and stayed at low levels

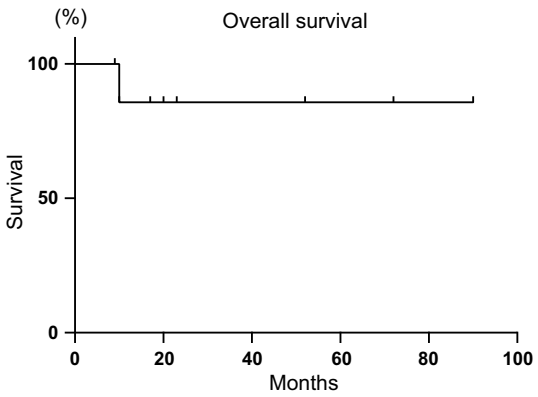

Fig. 4 Overall survival of the 8 patients with ALA who were treated with CyBorD

and quicker efficacy and less organ damage than high-dose melphalan with auto-PBSCT and warrants larger and more comprehensive trials.

Table 3 Adverse events

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutropenia	1	1	0	0	0
Anemia	5	1	1	0	0
Thrombocytopenia	5	1	0	0	0
Peripheral neuropathy	2	0	0	0	0
Diarrhea	1	2	0	0	0
Constipation/Ireus	0	1	2	0	0
Fever without Neutropenia	0	2	1	0	0
VZV recurrent infection	0	0	1	0	0
Heart	0	0	1	0	0
Kidney	2	0	0	0	0
Lung	0	1	0	0	0
Liver	5	0	0	0	0
Rush	1	0	0	0	0

Conflict of interest The authors declare no conflict of interest.

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