

Original

Therapeutic outcome of cyclic VAD (vincristine, doxorubicin and dexamethasone) therapy in primary systemic AL amyloidosis patients

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Abstract

Objective: Intensive chemotherapy targeting plasma cell dyscrasia has been recently employed for the treatment of primary systemic AL amyloidosis. We prospectively studied the clinical usefulness of cyclic VAD (vincristine, doxorubicin and dexamethasone) in patients with primary systemic AL amyloidosis who were ineligible for high-dose melphalan with autologous stem cell support.

Patients and methods: Eight patients (mean age, 60.4 ± 8.8 years) were treated with cyclic VAD until the disappearance of M-protein from both serum and urine. Of these, seven showed nephrotic syndrome before the start of VAD irrespective of a decrease in creatinine clearance. Serial follow-up studies after VAD evaluated hematological status and organ function.

Results: Four patients (50%) showed a marked decrease in abnormal plasma cells in the bone marrow and normalized κ/λ ratios of serum free light chain in conjunction with disappearance of M-protein after 1 to 3 courses of VAD. There were no serious adverse events, and nephrotic syndrome gradually improved with no hematological relapse in the follow-up period of 3 to 5 years. The remaining 4 patients showed worsening of congestive heart failure and/or systemic edema ascribable to dexamethasone, resulting in cessation of cyclic VAD before disappearance of M-protein. All of these patients died of multiple organ failure or required permanent hemodialysis within 1 year after the start of cyclic VAD.

Conclusions: Cyclic VAD is a potent therapeutic option in primary systemic AL amyloidosis, but in patients with renal or cardiac dysfunction careful management for adverse events, especially body fluid retention, is necessary.

Keywords: primary systemic AL amyloidosis, cyclic VAD (vincristine, doxorubicin and dexamethasone), plasma cell dyscrasia, nephrotic syndrome

INTRODUCTION

Primary systemic AL amyloidosis is an intractable disorder caused by plasma cell dyscrasia. Amyloid fibrils, formed by degradation of immunoglobulin light chains produced by abnormal plasma cells, gradually accumulate in multiple vital organs, including the heart, kidneys and gastrointestinal (GI) tract (1). To avoid progressive dysfunction of these organs, various chemotherapies targeting plasma cell dyscrasia have been employed for the treatment of primary systemic AL amyloidosis. Among them high-dose melphalan with autologous peripheral blood stem cell transplantation (auto-PBSCT) has been widely accepted as the most effective chemotherapy with regard to hematological response in the last decade (2). Nevertheless, this treatment has the disadvantage of high mortality ascribable to subclinical or overt dysfunction in multiple vital organs (3, 4). VAD (vincristine, doxorubicin and dexamethasone) is another intensive chemotherapy for primary systemic AL amyloidosis (5-7). In this study we performed cyclic VAD in Japanese patients with systemic AL amyloidosis according to criteria related to the severity of organ involvement. One half of the patients showed improvement of clinical symptoms, particularly nephrotic syndrome, after complete hematological remission, and we focus upon the clinical benefits and adverse effects of cyclic VAD.

PATIENTS AND METHODS

Patients

Eight patients with primary systemic AL amyloidosis (4 men and 4 women; age range, 45 to 71 years; mean, 60.4 ± 8.8 years), who were selected according to criteria reported by Gono et al (8), were enrolled in this study. None of the patients had received any medical treatment for plasma cell dyscrasia at enrollment. To detect amyloid deposition, alkaline Congo red staining was performed in more than 2 biopsied tissues, and in at least one of these specimens immunohistochemical staining was carried out

using different antibodies to AL κ , AL λ , amyloid A, transthyretin and β 2 microglobulin in order to confirm it as AL type (9). Multiple myeloma was excluded by a serum M-protein level of lower than 3.0 g/dl, plasma cells less than 10% of the total number of nucleated cells in the bone marrow and no osteolytic lesions on X-ray examinations according to the diagnostic criteria proposed by the International Myeloma Working Group (10). The percentage of plasma cells in the bone marrow was examined on smear specimens treated with Wright-Giemsa staining. To identify M-protein in serum and urine, immunofixation was performed in all the patients, and other information was obtained from their medical records. Free light chains (FLCs) in serum were simultaneously measured using a commercially available kit based on a latex-enhanced immunoassay (The Binding Site, Birmingham, UK) on a Behring BN II nephelometric analyzer (Dade Behring, Deerfield, IL, USA). Both κ - and λ -type FLCs were separately determined, and the κ/λ ratio was calculated. Normal values of the κ/λ ratio range from 0.26 to 1.65. At study entry the extent of amyloid-induced organ involvement was evaluated in each patient according to the clinical criteria proposed by Comenzo et al (11). The Local Ethical Committee approved this study.

Treatment

The VAD regimen was as follows: vincristine 0.4 mg/day and doxorubicin 9 mg/m²/day by continuous intravenous infusion on days 1-4 (total dose: vincristine 1.6 mg, doxorubicin 36 mg/m²), and dexamethasone 40 mg/day by intravenous infusion on days 1-4, 9-12 and 17-20 (total dose 480 mg). All treatments were repeated every 4 weeks until disappearance of M-protein from both serum and urine on immunofixation, which was defined as complete hematological remission, as long as there were no serious complications. Interferon- α was used at a dose of 3 MIU/week as a maintenance therapy after achieving complete hematological remission. M-protein was investigated on immunofixation at 3- to 6-month intervals after its disappearance. When M-protein reappeared in either serum or urine, readministration of VAD was actively considered.

Informed consent was obtained from all the patients before starting VAD.

Evaluation of therapeutic and toxic effects

Therapeutic effects of cyclic VAD were evaluated in terms of amyloidosis-related organ involvement, particularly renal function, and performance status of the patients. Because almost all the patients in this study showed nephrotic syndrome, we employed daily protein excretion in urine as well as total protein and albumin in serum as a therapeutic marker of renal involvement. Serum levels of brain natriuretic peptide (BNP) and echocardiographic examinations assessed cardiac involvement. A standard M-mode scan of the left atrium (LA) and ventricle (LV) was made in order to measure the thickness of the interventricular septum (IVS), fractional shortening of LV (FS), LV dimensions in the end-diastole and LA dimensions. The LV outflow tract velocity was recorded on pulsed Doppler, positioning the sample volume just below the aortic valve in the apical 4-chamber view. Analysis of Doppler flow was performed with computerized planimetry (Color Cineview Plus, TomTee Imaging Systems). Three or more consecutive beats were averaged for each measurement. To quantitatively evaluate diastolic function, we measured the peak velocities of early (E) and late filling (A) waves of transmitral flow (TMF), E/A ratio and deceleration time of E waves. The Southwestern Oncology Group (SWOG) criteria were used for evaluating performance status of the patients (12). Toxic effects were also assessed during and after the chemotherapy. Survival curves were constructed by Kaplan-Meier's method, depending on whether the patients achieved complete hematological remission or not. In these curves starting and end points were set at commencement of therapy and death, respectively.

Statistics

A log-rank test was employed for detecting a statistically significant difference between survival curves. A p-level less than 0.05 was considered to be statistically significant. Commercially available statistics software was used for data analysis

(StatView for Macintosh, Abacus Concepts, Berkeley, CA, USA).

RESULTS

Hematological response

Clinical profiles of the patients are shown in Table 1. Four of 8 patients had M-protein in serum, which was identified as IgG λ in 3 and IgA κ in 1 on immunofixation. Despite the absence of M-protein in serum, the remaining 4 patients showed BJP λ in urine. All of the patients demonstrated abnormal FLC κ/λ ratios in serum and clonal expansion of plasma cells in the bone marrow on flow cytometry except for case 6, in whom the FLC κ/λ ratio was within normal limits. The main clinical symptoms of the patients consisted of nephrotic syndrome in 7 patients (cases 1, 2, 4 to 8), amyloid cardiomyopathy in one (case 5) and urinary bladder hemorrhage in one (case 3). Case 5 showed both nephrotic syndrome and cardiomyopathy.

Cases 1 to 3 showed complete hematological remission with no serious adverse events after 2 or 3 courses of VAD. Case 4 achieved complete hematological remission after 1 course of VAD, but the second cycle of this chemotherapy could not be performed because of syncopal attacks ascribable to temporary worsening of cardiac and/or autonomic nerve function. Cases 2 to 4 were treated with interferon- α after achieving complete hematological remission, but case 1 refused this maintenance therapy. The administration of interferon- α was stopped in cases 2 and 3 because of adverse effects, such as thrombocytopenia and depression, at 48 and 12 months after commencement, respectively. Cases 1 to 4 showed no reappearance of M-protein in either serum or urine in the serial follow-up studies. The FLC κ/λ ratio was normalized in conjunction with the disappearance of M-protein in these 4 patients, and remained within almost normal levels for 4 years after cyclic VAD therapy (Fig. 1A).

The remaining 4 patients (cases 5 to 8) showed serious adverse events ascribable to VAD, such as encephalopathy, glucocorticoid-induced fluid retention and worsening

of renal and heart failure, and became unable to continue this therapy before the disappearance of M-protein. At cessation of VAD therapy, M-protein was detectable on immunofixation in these 4 patients, but the FLC κ/λ ratio was within normal limits in cases 6 and 8.

Survival curves

The patients were classified into remission (cases 1 to 4) and non-remission (cases 5 to 8) groups. Kaplan-Meier's survival curves of the 2 patient groups are shown in Fig. 2. The fifty-percent survival period was 7.0 ± 2.0 months for the non-remission group, while it could not be calculated for the remission group because all the patients are still alive. The numbers of patients alive 300 days after commencement of therapy were 4 in the remission group and only 1 in non-remission. Causes of death in the non-remission group were congestive heart failure in case 5 and uremia in cases 6 and 7. Case 8 in the non-remission group is still alive, but hemodialysis had to be started 330 days after commencement of VAD.

Therapeutic outcomes

Therapeutic outcomes in the remission group are shown in Fig. 1. Cases 1, 2 and 4 showed improvement of nephrotic syndrome with an increase in serum levels of total protein and albumin and a decrease of more than 50% in urinary protein excretion 1 year after VAD. Serum levels of BNP (normal <20 pg/ml) decreased from 84.9 pg/ml and 407.8 pg/ml to 38.0 pg/ml and 207.6 pg/ml in cases 2 and 4, respectively, 1 year after VAD. Nevertheless, no obvious change was seen in other cardiac indices, including the thickness of IVS, FS and TMF E/A, even 4 years after VAD. Performance status of the remission group was grade 1 or 2, and did not change during and after VAD. All patients in the non-remission group showed rapid worsening of performance status in parallel with an increase in urinary protein excretion and a decrease in serum albumin (data not shown).

DISCUSSION

VAD is widely used in multiple myeloma as a standard therapeutic regimen targeting abnormal plasma cells in the bone marrow. These cells usually exist also in a form of plasma cell dyscrasia in primary systemic AL amyloidosis, although the number is much lower than in multiple myeloma. Considering that immunoglobulin light chains secreted from abnormal plasma cells turn into amyloid with conformational change, VAD should also be effective also in primary systemic AL amyloidosis with regard both to reduction of the precursor protein and to avoiding progressive dysfunction of vital organs. To increase the possibility of complete hematological remission, VAD can be employed as pretreatment for high-dose melphalan with auto-PBSCT in primary systemic AL amyloidosis because of the absence of negative effects on mobilization of hematopoietic stem cells in addition to the rapid reduction of pathogenetic plasma cells (6-8, 13). Several recent reports have demonstrated that some patients with primary systemic AL amyloidosis show good therapeutic outcomes after cyclic administration of VAD alone (5, 14). In the present study cyclic VAD showed good therapeutic outcomes with respect to both hematological response and visceral organ function in half of the patients who were ineligible for high-dose melphalan with auto-PBSCT. Interferon- α has been reported to show a good therapeutic effect in primary systemic AL amyloidosis (15), and we tried to use this drug in our patients after VAD. Cases 2 to 4 were treated with interferon- α , but case 1 refused this maintenance therapy. Three patients with nephrotic syndrome showed an increase in serum levels of albumin in parallel with a decrease in daily protein excretion in urine after achieving complete hematological remission. Another notable point in our study is that complete hematological remission persisted for a long period after 1 to 3 courses of VAD irrespective of maintenance therapy with interferon- α . These good therapeutic outcomes may be partly ascribed to the small number of abnormal plasma cells in primary systemic AL amyloidosis. Abnormal plasma cells can be classified into several

subpopulations according to surface markers, and in multiple myeloma high proportions of the immature subtype have been reported to correlate well with a poor response to treatment (16, 17). Further studies are required in order to clarify whether subtypes of abnormal plasma cells are related to therapeutic outcomes also in primary systemic AL amyloidosis.

Doxorubicin and vincristine, which are included in the VAD regimen, can cause cardiac toxicity and neuropathy, respectively. VAD is, therefore, excluded as a therapeutic option in patients with primary systemic AL amyloidosis showing severe cardiac involvement and/or neuropathy. In our study cardiac involvement was present in 4 patients, but of these, 3 were considered to be eligible for VAD on the basis of well-preserved Doppler-based indices on echocardiography. The remaining 1 patient received 1 course of VAD at her request despite the presence of severe cardiac involvement. No patient showed any symptoms ascribable to polyneuropathy before or after cyclic VAD. The most notable point concerning adverse effects of VAD in our study is that corticosteroid-induced fluid retention was much more frequently seen than previously thought. Six patients in our study (75%) showed obvious corticosteroid-induced fluid retention. Among them, 4 had to discontinue cyclic VAD therapy before achieving complete hematological remission because of adverse events, such as intestinal pseudo-obstruction and congestive heart failure ascribable to an excess of body fluid. These 6 patients were considered to have more severe impairment of renal and/or cardiac function before starting VAD with regard to serum BNP, 24 hr creatinine clearance and daily protein excretion compared with the remaining 2 patients. As overt or subclinical visceral organ involvement often exists in patients with primary systemic AL amyloidosis, intensive management of body fluids is necessary during and after cyclic VAD therapy, particularly when marked hypoalbuminemia due to nephrotic syndrome and/or cardiac dysfunction are present. Cyclic VAD is risky in the advanced stage of primary systemic AL amyloidosis, and the enrollment criteria we employed in

this study may be helpful in selecting patients eligible for this intensive chemotherapy (8).

In conclusion, cyclic VAD therapy is effective for approximately 50% of patients with primary systemic AL amyloidosis, although corticosteroid-induced fluid retention frequently occurs as an adverse effect, particularly in those with severe nephrotic syndrome and/or cardiac dysfunction. This therapy should be actively considered as a therapeutic option when high-dose melphalan with auto-PBSCT is inappropriate because of advanced age or vital organ involvement.

Acknowledgments

The authors are grateful to Drs. Y. Hoshii and T. Ishihara, Department of Pathology, Yamaguchi University School of Medicine, for their help with immunohistochemical staining of the biopsy specimens, and also to Dr. T. Yamada, Department of Laboratory Medicine, Jichi University School of Medicine, for determination of the serum free light chain. This work was supported by a grant from the Intractable Disease Division, the Ministry of Health and Welfare, Research Committee for Epochal Diagnosis and Treatment of Amyloidosis in Japan.

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FIGURE LEGENDS

Figure 1: The free light chain (FLC) κ/λ ratio in serum was normalized in patients with primary systemic AL amyloidosis who achieved complete hematological remission with cyclic VAD, and remained within the relatively normal range for 4 years (A, broken line: upper and lower limits of FLC). Serum levels of total protein (C) and albumin (D) gradually increased in parallel with a decrease in urinary protein excretion (B) in these patients. Closed triangles: case 1, closed circles: case 2, open squares: case 3, closed squares: case 4.

Figure 2: Kaplan-Meier's survival curves of the remission and non-remission groups. Solid line: the remission group (n=4), broken line: the non-remission group (n=4). Censored patients are ticked along the survival curves.

Table 1. Clinical profiles of the patients and outcomes of cyclic VAD

Case	1	2	3	4	5	6	7	8	Normal values	
Age/sex	62/F	71/M	67/M	62/F	45/F	54/F	54/M	68/M		
Organ involvement										
Kidney	+	+	-	+	+	+	+	+		
Heart	+	+	-	+	+	-	-	-		
Urinary bladder hemorrhage	-	-	+	-	-	-	-	-		
Liver	-	-	-	-	-	-	-	-		
Performance status	1	1	1	2	3	2	3	2		
Laboratory data before VAD										
M-protein**	Serum IgG λ	IgG λ	-	IgA κ	-	-	-	IgG λ		
	Urine BJP λ	BJP λ	BJP λ	BJP κ	BJP λ	BJP λ	BJP λ	BJP λ		
FLC κ/λ ratio	Before treatment	0.16	0.15	0.01	14.8	0.006	0.30	0.14	0.17	0.26-1.65
	On finishing cyclic VAD	0.98	1.39	0.41	1.89	0.03	0.53	0.10	0.28	
Abnormal plasma cells in bone marrow (%)***	4.4	6.1	8.0	2.2	8.4	0.5	2.8	0.5	0	
Serum brain natriuretic peptide (pg/mL)	17.6	84.9	67.9	407.8	606.0	24.7	75.7	25.8	<20	
Serum albumin (g/dL)	2.5	2.9	4.4	1.7	4.0	2.3	1.8	1.7	4.2-5.1	
Blood urea nitrogen (mg/dL)	11	17	15	21	19	24	26	16	9-22	
Creatinine (mg/dL)	0.63	0.88	0.62	0.67	0.76	1.77	1.48	1.04	0.4-1.0	
24h creatinine clearance (L/day)	106.0	71.8	144.0	93.3	68.8	43.4	54.0	53.4	80-130	
Daily protein excretion (g/day)	3.5	4.0	0.1	3.5	2.3	6.6	17.6	6.5	0	
VAD cycles performed	2	2	3	1	1*	2*	2*	2*		
Complete hematological remission	+	+	+	+	-	-	-	-		
Maintenance therapy with interferon- α	-	+	+	+	-	-	-	-		
	Duration (months)	48	12	49****						
Adverse events	-	IP	-	Syncope	CHF	Fluid retention	RF	IP		
		Fluid retention		Fluid retention	Encephalopathy		Fluid retention	Fluid retention		

*cessation of cyclic VAD before complete hematological remission, **detected by immunofixation, ***detected by flow cytometry, ****still being administered.

BJP: Bence Jones protein, FLC: free light chain, IP: intestinal pseudo-obstruction, CHF: congestive heart failure, RF: renal failure

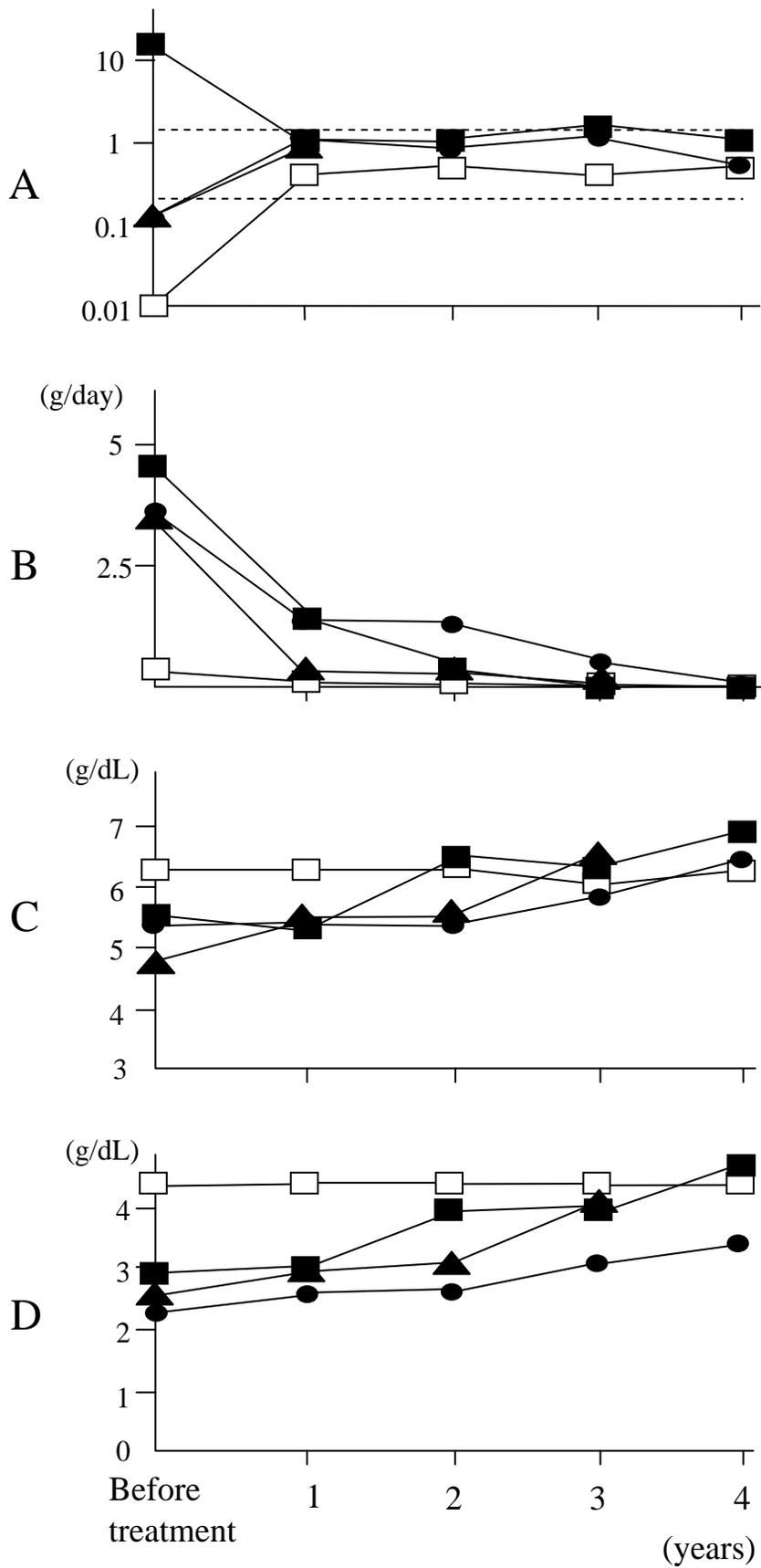


Figure 1

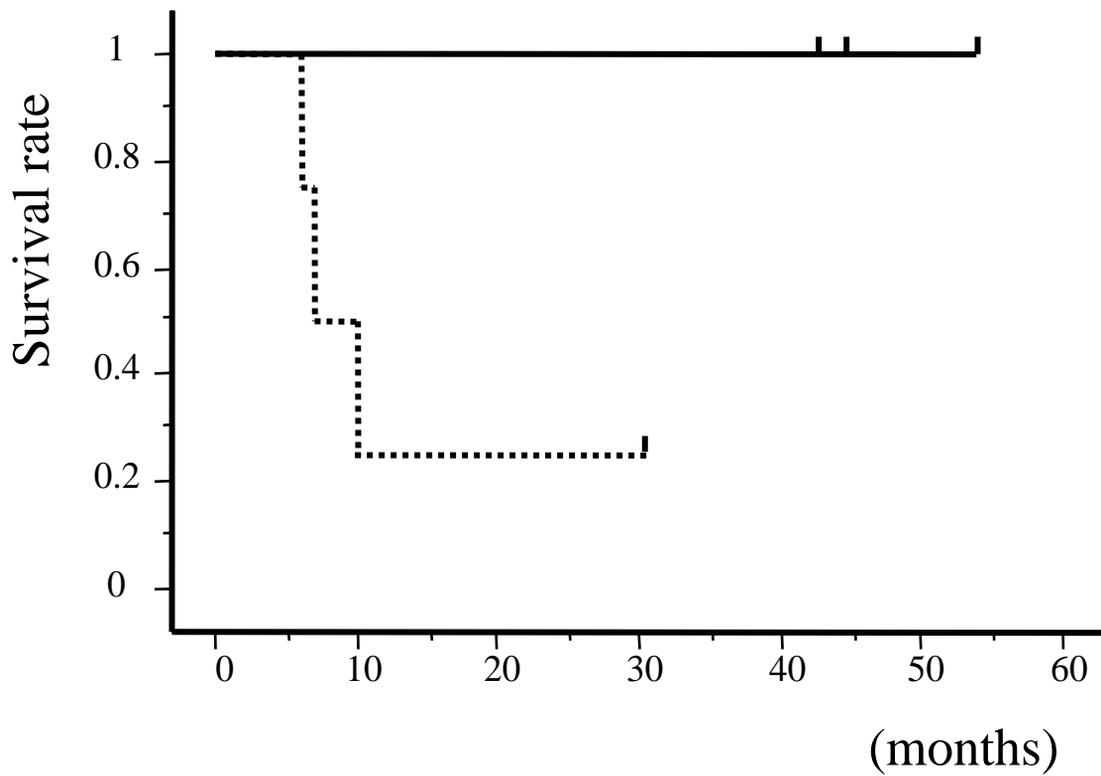


Figure 2