Successful Treatment of Amyloid Light-chain Amyloidosis in a Charcot-Marie-Tooth Disease Patient with Lenalidomide, Cyclophosphamide, and Dexamethasone

Yoshitaka Kikukawa¹, Hiroyuki Hata², Mitsuharu Ueda³, Taro Yamashita³, Singo Nasu¹, Kazuhiko Ide¹, Shikiko Ueno¹, Yukio Ando³, Hiroaki Mitsuya¹ and Yutaka Okuno¹

Abstract

A 70-year-old woman with Charcot-Marie-Tooth disease (CMT) suffered from nephrotic syndrome and a renal biopsy revealed non-AA amyloid depositions that contained immunoglobulin light chain λ . Her serum λ free LC was elevated to 80.8 mg/L and she was diagnosed with primary amyloid light-chain (AL) amyloidosis. She was subsequently treated with lenalidomide, cyclophosphamide, and dexamethasone (RCD). After 14 cycles of RCD, she achieved complete remission. Her serum albumin levels gradually normalized to 3.1 g/dL. No exacerbation of neurologic symptoms related to CMT was observed. Thus, RCD may be a well-tolerated and effective regimen for treating AL amyloidosis in patients with CMT disease.

Key words: AL amyloidosis, lenalidomide, RCD, Charcot-Marie-Tooth, neurotoxicity

(Intern Med 55: 2707-2712, 2016)

(DOI: 10.2169/internalmedicine.55.5815)

Introduction

Systemic amyloid light-chain (AL) amyloidosis is a rare disease characterized by amyloid deposits in the whole body, complicating monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, and Waldenström's macroglobulinemia. In MGUS and multiple myeloma, abnormal plasma cells produce immunoglobulin (Ig) light chain (LC), which becomes deposited in several organs, resulting in organ damage to the heart, kidney, liver, peripheral nerves, autonomic nerves, and many other organs. Cardiac amyloidosis is associated with a poor prognosis, with a mean overall survival of <1 year (1). Renal amyloidosis results in nephrotic syndrome, leading to severe edema, pleural and peritoneal effusions, and finally to renal failure requiring hemodialysis. The prognosis of AL amyloidosis in the absence of treatment is generally poor, and the response to conventional therapy (i.e., melphalan and dexamethasone combination therapy) is also poor. High-dose

melphalan with autologous peripheral blood hematopoietic stem cell transplant (PBSCT) has demonstrated a remission rate of approximately 50% (2, 3), however, patients older than 70 years of age or those with severe organ damage are ineligible for such treatment. Indeed, many patients with AL amyloidosis already have severe organ damage, including heart damage, at the diagnosis (4).

Several novel agents, including proteasome inhibitors bortezomib and carfilzomib and immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide, have recently become available for the treatment of multiple myeloma. These drugs can dramatically improve the prognosis and prolong the survival of myeloma patients. The three-drug combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD) has been reported to be highly effective in patients with AL amyloidosis (5-7). Mikhael et al. showed that approximately 70% of patients achieved complete remission (CR), with an overall response rate of 94% (6). We also previously found that CyBorD therapy resulted in CR in four, very good partial remission (VGPR) in

¹Departments of Hematology, Rheumatology, and Infectious Disease, Kumamoto University Graduate School of Medicine, Japan, ²Division of Informative Clinical Sciences, Faculty of Medical Sciences, Kumamoto University, Japan and ³Diagnostic Unit for Amyloidosis, Department of Neurology, Kumamoto University Hospital, Japan

Received for publication May 22, 2015; Accepted for publication February 1, 2016

Correspondence to Dr. Yutaka Okuno, yokuno@gpo.kumamoto-u.ac.jp

Table 1. Laboratory Data on Admission.

WBC	5,500 / μ L	TP	5.0 g/dL	T-CHO	223 mg/dL
Hgb	14.0 g/dL	Alb	1.7 g/dL	TG	137 mg/dL
Hct	43.4 %	Na	143 mEq/L	HDL-C	51 mg/dL
PLT	281×10^3 / μ L	K	4.7 mEq/L	LDL-C	145 mg/dL
PT	10.8 sec	Cl	113 mEq/L	TSH	2.43 μ U/mL
PT (INR)	0.91	BUN	12.3 mg/dL	BNP	45.2 pg/mL
APTT	41.9 sec	Crea	0.50 mg/dL	IgG	622 mg/dL
Fib	≥ 700 mg/dL	eGFR	89 mL/min/m ²	IgA	415 mg/dL
ATIII	97 %	T-Bil	0.4 mg/dL	IgM	241 mg/dL
$\alpha 2$ -PI	98 %	AST	29 U/L	Free κ chain	20.9 mg/dL
P-FDP	6.6 μ g/mL	ALT	15 U/L	Free λ chain	80.8 mg/dL
D-dimer	1.2 μ g/mL	LD	280 U/L	κ/λ ratio	0.261
TAT	1.24 ng/mL	ALP	499 U/L	d-FLC ^a	59.9 mg/dL
PIC	2.12 μ g/mL	CHE	624 U/L		
		CRP	0.40 mg/dL		

^ad-FLC: difference between involved and uninvolved FLCs

two, and partial remission in two of eight patients, with an overall response rate of 100% (7). The combination of lenalidomide, cyclophosphamide, and dexamethasone (RCD) was also reported to be effective in AL amyloidosis (8, 9). Kastritis et al. showed that RCD therapy achieved CR in 8% of patients, with an overall response rate of 55%, while Kumar et al. showed that RCD therapy achieved CR and VGPR in 11% (4/35) and 29% (10/35) of patients, respectively, with an overall response rate of 60% (21/35 patients) (8, 9).

Charcot-Marie-Tooth disease (CMT) is a hereditary autosomal dominant disease that leads to neuralgic amyotrophy. Neuropathic drugs are therefore contraindicated in patients with CMT (10, 11), thus limiting potential anticancer therapies (12, 13). Bortezomib and thalidomide are well known to have side effects of peripheral neuropathy (14-16). We herein report a patient with AL amyloidosis and CMT who was successfully treated with RCD therapy.

Case Report

A 70-year-old Japanese woman was admitted to our hospital due to severe upper and lower edema. She had been diagnosed with CMT approximately 10 years previously. She had edema of both lower limbs 8 months before this admission, and palpebral edema of both upper limbs had exacerbated over the previous 4 months. Blood tests were performed on admission (Table 1). Her serum albumin level was 1.7 g/dL and estimated urinary protein excretion was 6.87 g/day according to the urinary total protein creatinine ratio. She was diagnosed with nephrotic syndrome, and a kidney biopsy was subsequently performed (Fig. 1A). Congo red staining revealed orange-red deposits, which showed apple-green birefringence under polarized light, in the vascular walls and glomeruli. Amyloid deposits were also found in duodenum and rectum biopsy samples (Fig. 1B). These amyloid deposits were negative for staining with anti-amyloid A, transthyretin, and Ig LC λ and κ antibodies (Fig. 2). Laser microdissection and liquid chromatography-tandem mass spectrometry revealed that the

amyloid deposits contained high levels of Ig LC λ (Table 2). IgA- λ type M protein was also detected by serum immunoelectrophoresis and immunofixation assays, and the free λ chain levels were elevated (80.8 mg/dL). Plasma cells were not increased in the bone marrow (0.9%), and the patient was therefore diagnosed with primary AL amyloidosis complicating MGUS. We concluded that her nephrotic syndrome was caused by primary AL amyloidosis.

We evaluated other potential organ damage induced by AL amyloidosis. An echocardiogram demonstrated no thickening of the ventricular wall or a granular sparkling sign, which are typical features of cardiac amyloidosis, and the serum N-terminal of the prohormone brain natriuretic peptide levels were normal (193 pg/mL), suggesting no severe heart damage. An abdominal echogram revealed mild hepatomegaly, however, her serum alkaline phosphatase levels were not highly elevated (Table 1), also indicating no severe liver damage.

We decided to treat amyloidosis-induced nephrotic syndrome with chemotherapeutic agents. However, although CyBorD therapy is effective for AL amyloidosis (5-7), bortezomib is a well-known neurotoxic agent, and it was necessary to avoid neurotoxic agents due to her coexisting CMT disease. Similarly, thalidomide is a key drug for the treatment of multiple myeloma and has demonstrated efficacy in AL amyloidosis, however, it is also a known neurotoxic agent (14-16). We therefore opted for a lenalidomide-containing regimen. RCD therapy has previously been shown to achieve CR or VGPR in 40% of patients, with an overall response rate of 60% in patients with AL amyloidosis (9). In the previous study, the treatment schedule consisted of 4-week cycles of: lenalidomide given at 15 mg orally (PO) on days 1-21; cyclophosphamide 300 mg/m² PO given on days 1, 8, and 15; and dexamethasone 40 mg PO given on days 1, 8, 15, and 22 continuously every week. Because our case was a 70-year-old patient who suffered from severe edema and CMT, we decided to reduce the doses of treatment. RCD therapy was therefore initiated with starting doses of lenalidomide 10 mg daily for 21 days, and cyclophosphamide 300 mg and dexamethasone 20 mg on

Figure 1. A histopathological analysis revealed non-AA amyloid deposits in the kidney and duodenal and rectal mucosae. A: A histopathological analysis of a renal biopsy sample. Renal biopsy samples showed weak periodic acid-Schiff-positive staining in the vascular walls and the glomerular mesangium (upper left and right panels). Congo red staining revealed orange-red amyloid deposits in the vascular walls and glomeruli (lower left panel). Amyloid deposits in the vascular walls and glomeruli showed apple-green birefringence under polarized light (lower right panel). B: A histopathological analysis of duodenal and rectal mucosa samples. Endoscopic images of the descending part of the duodenum (upper left panel) and rectum (upper right panel). Congo red staining revealed orange-red amyloid deposits in the duodenum (lower left panel) and the rectum (lower right panel).

Figure 2. Immunohistochemical staining of amyloid deposits. AL-amyloid deposits were negative for transthyretin (upper right panel), serum amyloid A (lower left panel), Ig LC κ , and Ig LC λ (lower middle and right panels).

Table 2. Mass Spectrometry Analysis of the Amyloid Deposits.

Accession ^a	Description	#PSMs ^b	#AAs ^c
J00252	Immunoglobulin lambda light chain C region (IGLC1)	2	104
P02649	Apolipoprotein E	5	317
Q8IYA6-2	Isoform 2 of Cytoskeleton-associated protein 2-like	3	334
P06702	Protein S100-A9	1	114
Q96KK5	Histone H2A type 1-H	1	128
P78539-3	Isoform 3 of Sushi repeat-containing protein SRPX	2	405
Q03591	Complement factor H-related protein 1	1	330
P08123	Collagen alpha-2 (I) chain	4	1,366
Q9P0M6	Core histone macro-H2A.2	1	372
P06727	Apolipoprotein A-IV	1	396
P22894	Neutrophil collagenase	1	467
P17661	Desmin	1	470
P04004	Vitronectin	1	478
P15502-7	Isoform 7 of Elastin, <i>Homo sapiens</i>	1	677
P01024	Complement C3	2	1,663
P12111-2	Isoform 2 of Collagen alpha-3 (VI) chain, <i>Homo sapiens</i>	1	2,971
P98160	Basement membrane-specific heparan sulfate proteoglycan core protein	1	4,391

^aAccession number according to the International Nucleotide Sequence Database.

^bPeptide spectrum matches. The total number of peptide spectra matched to predicted spectra according to the database.

^cThe total number of amino acids found within peptide spectrum matches.

days 1, 8, and 15. Lenalidomide was finally increased to 15 mg daily. Her free λ chain level was normalized after five cycles of RCD therapy (Fig. 3). After 14 cycles of RCD therapy, her serum immunofixation test became negative for IgA- λ M protein, indicating CR. Treatment was then stopped. Her serum albumin levels gradually increased from 1.7 g/dL to 3.1 g/dL, and her urinary protein creatinine ratio improved from 6.87 to 2.67.

She experienced no progression of either muscle weakness or amyotrophy, and no sensory impairment. The most notable adverse event was Common Terminology Criteria for Adverse Events (CTCAE) grade 2 diarrhea, which developed during the fourth treatment cycle, requiring discontinuation of the RCD regimen for 5 weeks until diarrhea disappeared. Treatment was then restarted with lenalidomide 5 mg daily, gradually increased to 15 mg daily (Fig. 3), with

Figure 3. Clinical course of the patient. After introduction of the RCD regimen, free λ chain was normalized to <30 mg/L in 3 months and the serum albumin levels gradually increased to 3.1 g/dL in 18 months. Grade 2 diarrhea appeared during the fourth cycle treatment and RCD was temporarily discontinued for 5 weeks until diarrhea resolved.

no recurrence of diarrhea. The only other adverse event was dysgeusia (CTCAE grade 1).

Discussion

We herein report the case of a 70-year-old Japanese woman with AL amyloidosis accompanying CMT disease, which was successfully treated with a RCD regimen resulting in hematological CR and recovery of kidney damage. There was no exacerbation of neurologic symptoms after AL amyloidosis onset in this patient, and no neuropathic progression after RCD treatment.

There are several current treatment options for AL amyloidosis. High-dose melphalan with PBSCT is an effective therapy for AL amyloidosis, however, patients with organ damage, especially heart impairment, are ineligible for this treatment (17). In addition, only approximately 50% of patients demonstrate a hematological response. Palladini et al. reported that melphalan and dexamethasone (MDex; dexamethasone 40 mg for 4 days) was highly effective in patients with AL amyloidosis, with CR and VGPR in terms of the hematological response of 31% and 29% of the patients, respectively (18). In contrast, CR and VGPR were reduced to 12% and 20%, respectively, with attenuated MDex (dexamethasone 20 mg for 4 days). Due to the patient's age and severe edema, we had to reduce the dose of dexamethasone, and therefore, we decided not to use MDex in the current patient.

Novel drugs, including the proteasome inhibitors bortezomib and carfilzomib and the immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide, have recently

become available for the treatment of myeloma patients, resulting in an improvement in the 5-year survival rate from 25.6% in 1989 to 44.9% in 2005. Regimens containing these novel agents have also been reported to be highly effective for AL amyloidosis. Kumar et al. reported that the RCD regimen was effective for AL-amyloidosis patients and obtained organ responses in eight (31%) of 26 patients with renal involvement (9). Palladini et al. also reported a phase II prospective trial of RCD in 21 patients with refractory or relapsed AL amyloidosis. The hematologic response rate was 62%, with one CR and five VGPRs. The achievement of CR/VGPR was associated with a significant survival advantage. Severe adverse events occurred in 57% of the patients, however, there were no severe neurological events and no deaths during treatment (19).

CMT is a progressive neuralgic amyotrophic disease, and more than 75 genes responsible for CMT have been identified (20). CMT has a very slow disease progression and a relatively good prognosis. However, because CMT patients tend to live longer, they may also suffer from several malignant neoplasms, in which case the potential neurotoxicity of anticancer agents becomes a matter for concern. Anticancer drugs have been reported (21) to induce severe neuralgic amyotrophy, and vincristine, one of the most neurotoxic agents, induces severe peripheral neuropathy (10, 11). Weimer et al. described medication-induced exacerbation of neuropathy in CMT and proposed a list of medications of concern for patients with CMT. Vincristine was listed as "Definite high risk (including asymptomatic CMT)" and bortezomib and thalidomide were also listed as "Moderate to significant risk" (21). Aging of CMT patients may also

result in emergencies of plasma cell dyscrasia, including MGUS and multiple myeloma. Because AL amyloidosis is a complication of MGUS and multiple myeloma, aged CMT patients may also develop AL amyloidosis, as in the current case. Bortezomib is contraindicated in CMT due to its neurotoxicity, and while thalidomide is also neurotoxic, only a few reports have indicated its efficacy in AL amyloidosis (15, 16). We therefore chose the lenalidomide-containing regimen RCD in the current case. Five cycles of RCD therapy resulted in normalization of the free λ chain levels, while 14 cycles induced CR, with no progression of CMT, including neuralgic amyotrophy or sensory impairment, during and after RCD therapy. RCD may thus be a safe and effective regimen for treating AL amyloidosis, and possibly myeloma, in patients with CMT. This case provides the first report of a patient with both CMT and AL amyloidosis and highlights the treatment options in patients with these conditions.

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

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