

[ORIGINAL ARTICLE]

Nationwide Survey of 741 Patients with Systemic Amyloid Light-chain Amyloidosis in Japan

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Abstract:

Objective To retrospectively investigate the clinical manifestations of systemic amyloid light-chain (AL) amyloidosis in Japanese patients and the treatment strategy for the condition.

Methods We conducted a survey of Japanese AL amyloidosis patients, who were treated between January 1, 2012, and December 31, 2014.

Results A total of 741 AL amyloidosis patients were included in this study (436 men and 305 women; median age: 65 years old, range: 31-93). The most frequently affected organ was the kidneys (n=542), followed by the heart (n=252), gastrointestinal (GI) tract (n=164), autonomic nervous system (n=131), liver (n=71), and peripheral nervous system (n=71). Diagnostic findings were most commonly detected in the GI tract (upper GI tract: 350 cases, lower GI tract: 167 cases), followed by the bone marrow and kidneys. An abdominal fat-pad biopsy was only conducted in 128 patients. Autologous stem cell transplants (ASCTs) and bortezomib were used to treat 126 and 276 patients, respectively.

Conclusion The clinical features of Japanese patients with systemic AL amyloidosis are similar to those reported previously for cases in the US and Europe. Regarding treatment, a significant number of ASCTs were performed in Japan as well as in Western countries. Surprisingly, a marked number of patients received bortezomib as a treatment for AL amyloidosis.

Key words: systemic AL amyloidosis, clinical manifestation, treatment modality, Japanese patients

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Introduction

Amyloidoses are protein conformational diseases caused by the misfolding and aggregation of autologous proteins, which are deposited in tissues in the form of amyloid fibrils (1). Currently, 31 different proteins have been identified as possible causes of amyloidosis (2). Amyloid light-chain (AL) amyloidosis is a multi-systemic disorder caused by a malignant plasma cell clone that results in insoluble fibrillary deposition (3, 4). Amyloid fibrils derived from

misfolded immunoglobulin light chains cause direct organ toxicity, leading to organ failure and death. The most commonly affected organs are the heart, kidneys, gastrointestinal (GI) tract, liver, and the peripheral and autonomic nervous systems (4-6).

Although AL amyloidosis is the most common form of systemic amyloidosis [incidence: approximately 1 case per 100,000 person-years in the US (4)], there is little information available concerning the status of AL amyloidosis, such as its incidence, the demographic features of AL amyloidosis patients, and the treatment strategy for the condition, in

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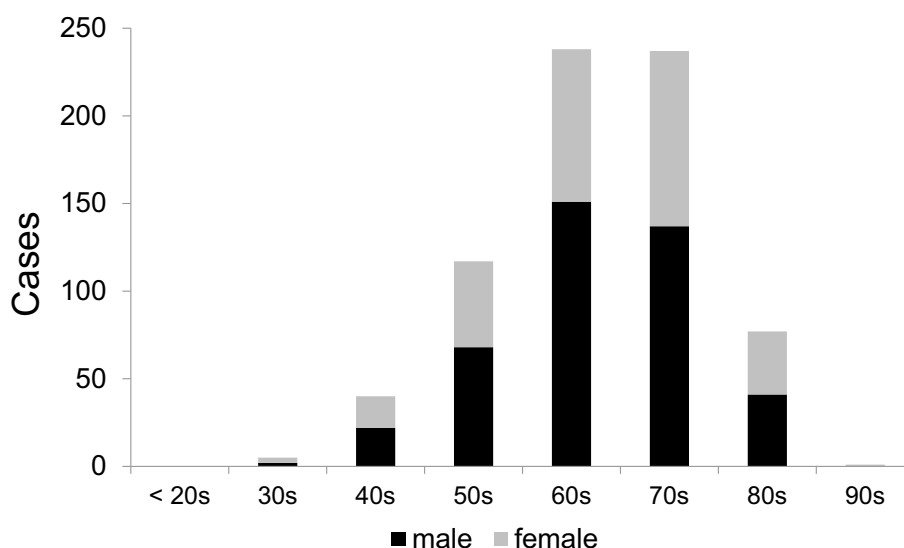


Figure 1. Age and sex distribution at the diagnosis in 711 Japanese patients with AL amyloidosis. Thirty patients were excluded because no data were reported for them. Their median age was 65 years old, and 64% of the patients were ≥ 65 years old.

Japan (7). Therefore, the Amyloidosis Research Committee, Intractable Disease Division, of the Japanese Ministry of Health and Welfare conducted a nationwide survey of AL amyloidosis in Japan.

Materials and Methods

A survey of AL amyloidosis patients treated between January 1, 2012, and December 31, 2014, was conducted by the Amyloidosis Research Committee, Intractable Disease Division, of the Japanese Ministry of Health and Welfare. The survey was sent to 4,652 hospital departments, including departments of neurology, gastroenterology, cardiology, neurosurgery, urology, rheumatology, hematology, and renal disease, which were randomly selected from all hospitals in Japan according to the number of hospital beds. Sampling fractions were as follows: 2.5% for general hospitals with 99 or fewer beds; 5% for 100 to 199 beds; 10% for 200 to 299 beds; 20% for 300 to 399 beds; 40% for 400 to 499 beds; and 100% for 500 or more beds, university hospitals and special hospitals in which the patients with amyloidosis were very likely to visit irrespective of the number of beds. Responses were obtained from 2,321 departments (49.9%). A total of 1,494 cases were identified by the primary survey, and 741 cases of AL amyloidosis were collected during the secondary survey.

The study was approved by the institutional review board of Kumamoto University, Kumamoto and Japan Community Health care Organization Kyoto Kuramaguchi Medical Center, Kyoto.

Results

A total of 741 AL amyloidosis patients were included in this study (436 males and 305 females; median age: 65

years old, range: 31-93 years old) (Fig. 1). Patients ≥ 65 years of age accounted for 64%.

Initial symptoms

The clinical manifestations at the diagnosis of the 741 patients are summarized in Fig. 2. Regarding cardiac damage, conduction disturbances were seen in 64 (10.3%) of 618 patients. First-degree atrioventricular (AV) block was observed in 31 patients, sinus failure was detected in 21 patients, and cardiac arrhythmia was seen in 80 patients (atrial fibrillation and flutter: 53 patients, ventricular tachycardia and flutter: 18 patients). Cardiac failure was seen in 156 (28%) of 566 patients. Of these, 70 patients suffered cardiac failure of worse than grade 3 according to the New York Heart Association (NYHA) classification.

Proteinuria was detected in 487 patients. Renal failure was seen in 250 patients, and 89 of these patients had an estimated glomerular filtration rate (eGFR) of <30 mL/min/ 1.73 m². Twenty-five patients were receiving dialysis.

Sensory nerve disturbance was seen in 71 patients, and more than half of these cases involved disturbance of the lower extremities. Autonomic nerve disturbance was more common (orthostatic hypotension: 107 patients; dysuria: 23 patients). The following GI tract symptoms were detected: diarrhea, 81 patients; constipation, 71 patients; GI bleeding, 45 patients; ileus, 9 patients; and protein-losing gastroenteropathy, 5 patients. Carpal tunnel syndrome was observed in 44 patients, and the shoulder-pad sign was seen in 3 patients. As for organomegaly, hepatomegaly was the most commonly observed type of organomegaly (71 patients), followed by splenomegaly (40 patients), macroglossia (66 patients), thyroid swelling (15 patients), submandibular swelling (10 patients), and lymph node swelling (35 patients).

The number of involved organs was one in 321 patients, two in 220 patients, and ≥ 3 in 131 patients. The most fre-

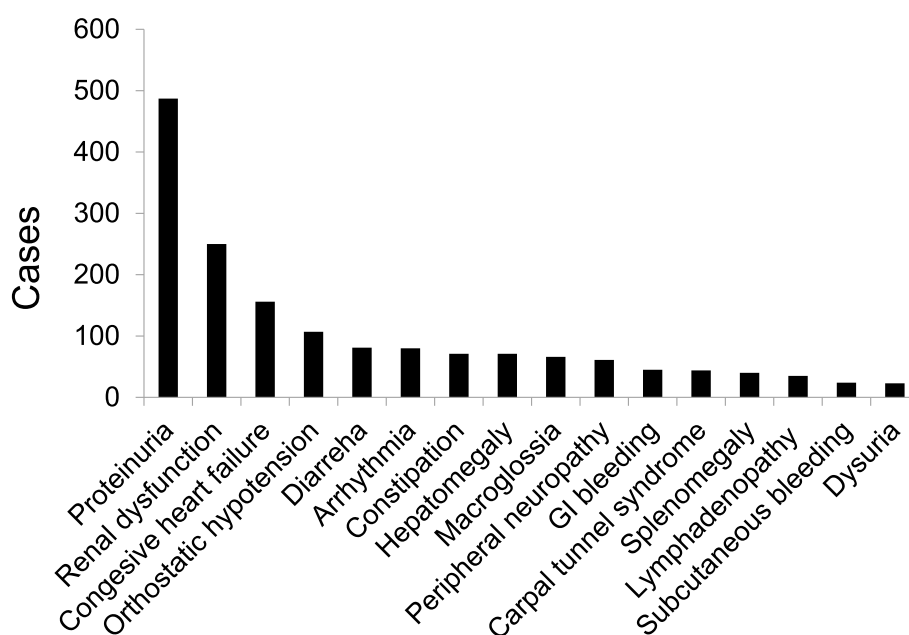


Figure 2. Clinical manifestations at the diagnosis in 741 Japanese patients with AL amyloidosis. Proteinuria was the most common manifestation, followed by renal dysfunction, congestive heart failure, orthostatic hypotension, diarrhea, arrhythmia, and constipation.

Table 1. Patient Characteristics.

Characteristic	n=741
Age, years, median (range)	65 (31-93)
Age ≥65 years, N (%)	460 (64%)
Male sex, N (%)	436 (59%)
Organ involvement, N	
≥3 organs	131
2 organs	220
1 organ	321
Kidneys	542
Heart	252
Gastrointestinal tract	164
Liver	71
Autonomic nervous system	131
Peripheral nervous system	71
Lymph nodes	35
M protein (IgG/IgA/IgM/BJP)	145/69/16/381
Lambda restricted, N (%)	221 (78%)
FLC lambda, mg/L, N	152 (1.7-11,200), 221
FLC kappa, mg/L, N	301 (2.5-13,200), 64
BMPC, median (range)	5 (0-91)
NT-proBNP, pg/mL, median (range), N	2,801 (113-79,000), 105
NT-proBNP ≥8,500 pg/mL, N (%)	21 (20%)
Troponin T, ng/mL, N	0.054, 189
UCG	
Granular sparkling sign, N (%)	152 (31%)
IVST, mm, median (range), N	13 (7-24), 220
Urinary protein, g/gCr, N	4.8 (0-26), 224

N: number, BJP: Bence-Jones protein, FLC: free light chain, BMPC: bone marrow plasma cells, NT-proBNP: N-terminal fragment of the pro-brain natriuretic peptide, UCG: ultrasound cardiogram, IVST: intraventricular thickness

Table 2. Biopsy Site for a Diagnosis.

Site	Cases	Positive cases, N (%)
Gastrointestinal (GI) tract	424	224 (72%) of 310 cases
Upper GI tract	350	
Lower GI tract	167	
Abdominal fat pad	128	68 (53%)
Labial salivary gland	23	13 (70%)
Heart	78	67 (86%)
Kidneys	229	214 (93%)
Bone marrow	380	75 (20%)
Others	85	65 (76%)

N: number

quently affected organ was the kidneys (542 cases), followed by the heart (252 cases), GI tract (164 cases), autonomic nervous system (131 cases), liver (71 cases), peripheral nervous system (71 cases), and lymph nodes (35 cases) (Table 1).

Diagnoses

Biopsy examinations of the GI tract were performed in 424 patients [the upper GI (the stomach and duodenum) in 350 patients and the lower GI in 167 patients] (Table 2). Amyloid deposition was detected in 224 of 310 reported cases (72%).

An abdominal fat-pad biopsy was performed in 128 patients, and amyloid deposits were detected in 68 patients (53%). Cardiac biopsies were conducted in 78 patients, and amyloid deposits were detected in 67 patients (86%). Renal biopsies were carried out in 229 patients, and amyloid deposits were detected in 214 patients (93%). Bone marrow biopsies were performed in 380 patients, and amyloid deposits were detected in 75 patients (20%) (Table 2). Other

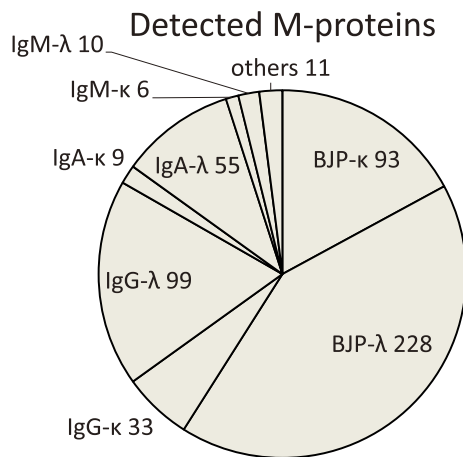


Figure 3. The type of detected serum M protein. λ type is more common than κ type in all immunoglobulin subclasses.

biopsy sites included the skin (33 patients), liver (20 patients), lungs (12 patients), tongue (11 patients), lymph nodes (8 patients), muscle (5 patients), mediastinal tumors (4 patients), bladder (4 patients), and laryngopharynx (4 patients).

Immunohistochemical staining of the κ and λ light chains was performed to diagnose AL amyloidosis in 392 patients, while a proteomic analysis based on liquid chromatography/tandem mass spectrometry (LC-MS) of tissue samples obtained via laser microdissection was conducted in 33 cases.

Laboratory findings

Ultrasonic cardiograms showed granular sparkling in 152 of 483 patients (32%). The median thickness of the intra-ventricular septum was 13 mm (7-24) in 220 patients with cardiac amyloidosis.

Electrocardiogram examinations showed AV block in 47 (8%) of 610 patients, sinus failure in 19 (3%) of 586 patients, and arrhythmia in 129 (20%) of 645 patients. The other findings included low-voltage in 16 patients, sinus bradycardia in 10 patients, ventricular extrasystole in 10 patients, and ST-T abnormalities in 7 patients.

The patients with cardiac amyloidosis exhibited increased median N-terminal fragment of the pro-brain natriuretic peptide (NT-proBNP) and cardiac troponin T levels (2,801 pg/mL and 0.054 ng/mL, respectively) (Table 1). Cardiac magnetic resonance imaging (MRI) showed late-contrast enhancement in 44 (48%) of 91 patients and cardiomegaly in 51 of 84 patients.

Bone marrow aspiration detected a median plasma cell frequency of 5% (0-91.6%) in 593 patients.

The type of serum M protein was Bence-Jones protein (BJP)- λ in 228 patients, BJP- κ in 93 patients, IgG in 145 patients (λ 99, κ 33), IgA in 69 patients (κ 9, λ 55), IgM in 16 patients (λ 10, κ 6), and others in 11 patients (Fig. 3). BJP was detected in urine in 350 (59%) of 597 patients; 259 (74%) patients exhibited the λ isotype (Fig. 3).

The serum free light chain (FLC) level was assessed in

Table 3. Treatment for AL Amyloidosis.

Treatment	Cases	Response, N		
		\geq PR	\geq VGPR	NR
MD	243	79	44	87
Bortezomib-based	276	110	60	61
Thalidomide-based	77	9	5	19
Lenalidomide-based	42	22	15	25
ASCT	126	92	73	26

MD: melphalan/dexamethasone, ASCT: autologous stem cell transplant, PR: partial response, VGPR: very good partial response, NR: not reported

285 patients. The median FLC- λ level was 152 (1.7-11,200) mg/L in 221 patients with λ AL, and the median FLC- κ level was 301 (2.5-13,200) mg/L in 64 patients with κ AL.

Treatment

Melphalan/dexamethasone (MD) was administered to 243 (63%) of 388 patients. Response was not reported in 87 patients. It was therefore difficult to calculate the correct overall response rate, but partial responses (PR) were obtained in 35 patients, very good partial responses (VGPR) were seen in 10 patients, and complete responses (CR) were achieved in 34 patients. Organ responses were seen in the heart in 20 patients and the kidneys in 46 patients (Table 3).

Bortezomib-based regimens were administered to 276 patients. Response was not reported in 61 patients. PR was obtained in 50 patients, VGPR was seen in 20 patients, and CR was achieved in 40 patients. Organ responses were seen in the heart in 23 patients, the kidneys in 62 patients, the liver in 6 patients, and the nervous system in 2 patients. Thalidomide-based regimens were administered to 77 patients. Response was not reported in 19 patients. However, PR was obtained in 4 patients, VGPR was seen in 2 patients, and CR was achieved in 3 patients. Organ responses were noted in the heart in 2 patients and the kidneys in 4 patients. Lenalidomide-based regimens were administered to at least 42 patients, and PR was obtained in 7 patients, VGPR was seen in 3 patients, and CR was achieved in 12 patients.

Autologous stem cell transplant (ASCT) was performed in 126 of 741 patients (17%). The \geq VGPR response rate was 58% (73 of 126 patients). Organ responses were seen in the heart in 15 patients, the kidneys in 47 patients, the liver in 5 patients, and the nervous system in 1 patient (Table 3).

Pacemakers were implanted in 39 patients, and cardiac defibrillators were implanted in 12 patients. Carpal tunnel release was performed in 18 patients.

Discussion

This is the first and largest nationwide survey of AL amyloidosis in Japan. It included more than 700 patients. Although this study was based on a retrospective survey, it

will help clarify the status of AL amyloidosis in Japan by providing information about the incidence of AL amyloidosis, the demographic features of AL amyloidosis patients, and the treatment strategy for the condition.

Clinical manifestations

The median age of 65 years detected in this study is similar to that described in previous studies conducted in Italy (62 years) and the US (63 years) (5, 8), but this study included older AL amyloidosis patients (≥ 65 years) than the recent studies performed by the Mayo Clinic (44%) and Shinshu University Hospital (7, 8). This is probably because the Mayo Clinic and Shinshu University Hospital are referral centers for amyloidosis, and only select patients are sent there, while this study involved a nationwide survey.

According to the survey, the most commonly affected organs were the kidneys, followed by the heart, GI tract, autonomic nervous system, peripheral nervous system, and liver. These findings are similar to those reported previously in the US and Europe and also agree with a report from a single institution in Japan (4-8). In the studies conducted in the US and Europe, the most commonly affected organs were the kidneys and the heart, respectively (5, 6, 8). The most common symptoms arising from these organs were a normal ejection fraction with diastolic dysfunction or left ventricular hypertrophy combined with a low-voltage electrocardiogram, nephrotic syndrome combined with a preserved glomerular filtration rate, purpura (most notably around the eyes and neck), small fiber peripheral neuropathy characterized by dysesthesia, orthostatic hypotension, and hepatomegaly (often combined with an elevated alkaline phosphatase level) (6). Although the GI tract commonly produces positive biopsy findings, it is relatively rare for patients to have GI symptoms.

More than 2 organs were affected in 52% of cases (351 of 672 cases) in this survey. This incidence rate is similar to that described in the report by Obici et al., in which more than 2 organs were affected in 69% of patients (5). However, a recent study by the Mayo Clinic demonstrated that patients diagnosed between 2010 and 2014 were less likely to have extensive organ involvement (defined as more than 2 affected organs) than patients treated during the 2005-2009 and 2000-2004 periods (15% vs. 24% vs. 20%, respectively) (8). Recognizing amyloidosis is the first step to obtaining a correct diagnosis, and educational programs for physicians aimed at increasing awareness of AL amyloidosis might contribute to an early diagnosis.

Diagnoses

It is recommended that subcutaneous fat aspiration (SFA) and bone marrow biopsies be performed to pathologically diagnose AL amyloidosis. These two procedures are easy to perform, carry little risk for patients, and have a combined diagnostic sensitivity of 85% (9). Alternatively, performing a biopsy of one of the affected organs will increase the diagnostic yield to 90-95% (4), but this approach must be

weighed against the risks associated with carrying out a more invasive procedure. Testing for amyloid in affected organs, such as the heart or kidneys, exhibits high sensitivity for detecting AL amyloidosis, as reported previously. Salivary gland biopsies might also be useful, especially if SFA produces a non-diagnostic or negative result (10). However, few patients undergo salivary gland biopsies in Japan (11).

In this survey, the diagnosis of AL amyloidosis was made using immunohistochemical typing in about half of patients (53%). Immunohistochemistry is widely available, but its specificity and sensitivity might be affected by the lack of standardized antibodies and non-specific absorption by amyloid fibrils; however, in experienced centers it might be highly sensitive and specific. Therefore, clinicians are encouraged to consult the amyloidosis medical practice centers at Kumamoto and Shinshu Universities when attempting to differentiate between the various types of amyloidosis.

Mass spectrometry can definitively identify amyloid fibril proteins in formalin-fixed tissue biopsy samples, and the combined use of laser microdissection and mass spectrometry enables the precise identification of the type of amyloid present in most cases (12). In the 21st century, mass spectrometry is the preferred method for typing amyloid proteins from tissue samples. However, this method is not widely used in Japan, and only 33 cases have been diagnosed using this technique.

Laboratory findings

In the cases examined in the present study, the patients' electrocardiograms exhibited abnormalities, such as low voltage and arrhythmia, and echocardiography showed thickening of the intraventricular septum and granular sparkling, as was reported previously (5-7). Recently, NT-proBNP and cardiac troponin T levels have been used as prognostic biomarkers, and a cardiac staging system based on the levels of these proteins has been proposed (13, 14). In the present study, the patients with cardiac amyloidosis displayed increased median NT-proBNP and cardiac troponin T levels. Cardiac MRI has recently been used to diagnose cardiac amyloidosis (15). Late-contrast enhancement is reported to be characteristic of cardiac amyloidosis, but thus far, few patients have been diagnosed with cardiac amyloidosis using MRI in Japan.

In the current study, the serum FLC level was measured in 285 patients, and the concentration of the λ type was found to be much higher than that of the κ type (κ : λ = 64: 221). The κ to λ ratio was approximately 3.5, which is similar to the ratios described in previous reports from Western countries (8).

Treatment of AL amyloidosis

MD is considered to be the standard treatment for AL amyloidosis. It is well tolerated and associated with good hematological and organ response rates of 67% and 33%, respectively (16). The median progression-free survival (PFS) and overall survival (OS) periods for AL amyloidosis

patients who receive such treatment are 3.8 and 5.1 years, respectively. This result was confirmed by a French prospective randomized trial comparing MD with ASCT (17). In total, 243 patients received MD in Japan during the study period.

One of the most interesting findings of this survey is that bortezomib is also widely used in Japan. Bortezomib-based regimens were administered to 276 patients. Although no randomized studies of this treatment strategy have been reported, the administration of bortezomib in combination with dexamethasone or alkylators was shown to increase the frequency of stronger hematological responses, and these regimens are currently the most commonly used induction regimens (18-20). A recent analysis performed at the Mayo Clinic showed that 65% of the AL amyloidosis patients diagnosed between 2010 and 2014 received bortezomib-based regimens, while 79% of the patients diagnosed between 2005 and 2009 received MD (8). Several studies of the use of bortezomib-based regimens to treat Japanese AL amyloidosis patients have been reported (21-23). These observations suggest that bortezomib should be approved for use in the government-sponsored health insurance system in the near future.

Thalidomide- and lenalidomide-based regimens are not used very often in Japan. These immunomodulatory drugs are less effective and less well tolerated in AL patients than in myeloma patients, but they remain effective treatment options for some patients (24, 25).

The role of ASCT is controversial. A prospective randomized trial comparing ASCT with MD showed that ASCT resulted in an inferior survival (17). The inferior outcomes were related to high early mortality in the ASCT arm (24%) and partly contributed to the inclusion of patients with severe cardiac amyloidosis and might also have been related to the inclusion of low-volume amyloid transplantation centers. A retrospective analysis of 1,536 patients with AL amyloidosis who underwent ASCT at 134 centers in North America conducted by the Center for International Blood and Marrow Transplant Research (IBMTR) showed that the 5-year OS rate improved from 55% in the period from 1995 to 2000 to 61% in the period from 2001 to 2006 and to 77% in the period from 2007 to 2012 (26). Furthermore, the mortality rate on day 100 progressively declined from 20% in the period from 1995 to 2000 to 11% in the period from 2001 to 2006, and then to 5% in the period from 2007 to 2012. In the multivariable analysis conducted in the latter study, cardiac AL was found to be associated with high early mortality and an inferior PFS and OS. Furthermore, ASCT in the period from 2007 to 2012 and the use of higher dosages of melphalan were demonstrated to be associated with a low risk of relapse, and a Karnofsky score of <80 and creatinine levels of ≥ 2 mg/dL were associated with a poor OS (26). Our data showed that a substantial number of ASCTs were performed in AL amyloidosis patients in Japan, as was reported recently (27, 28). Currently, it seems reasonable to consider ASCT for the approximately 20% of

patients who are young, have not had previous amyloid-related GI bleeding or clinically significant autonomic disease, have a good performance status, have not suffered advanced renal failure or recurrent symptomatic amyloid-related pleural effusion, and have a troponin T level of <0.06 ng/mL and an NT-proBNP level of <590 pmol/L (29). Further refinement of the patient selection methods and improvements in peri-transplant supportive clinical management remain priorities.

In summary, we have outlined the current status of AL amyloidosis in Japan. Although this was a retrospective survey, it was the first and largest nationwide survey and obtained the following important findings: 1) the clinical manifestations of Japanese AL amyloidosis patients are similar to those reported in Western countries; 2) Japanese AL amyloidosis patients exhibited more extensive organ involvement than the patients referred to the Mayo Clinic, suggesting that educating physicians to increase their awareness of AL amyloidosis is important and will lead to improved outcomes; and 3) bortezomib is more widely used than expected in Japan, suggesting that bortezomib should be covered by the government-sponsored health insurance system in the near future.

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

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