The Clinical Presentation and Management of Systemic Light-Chain Amyloidosis in China

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Key Words

Autologous stem cell transplantation · Chemotherapy · China · Clinical presentation · Systemic light-chain amyloidosis

Abstract

Background: Amyloidosis includes a group of diseases characterized by the extracellular deposition of various fibrillary proteins that can autoaggregate in a highly abnormal fibrillary conformation. The amyloid precursor protein of systemic light-chain (AL) amyloidosis is comprised of monoclonal light chains that are due to plasma cell dyscrasia. The clinical presentation of patients with AL amyloidosis varies from patient to patient. Current treatment strategies target the clone in order to decrease the production of the pathologic light chains. Recent advances in therapy have helped many patients with AL amyloidosis achieve hematologic and organ responses. **Summary:** AL amyloidosis is the most common type of systemic amyloidosis in China with increasing morbidity and a high mortality rate. The clinical presentation of AL amyloidosis is variable, and the median overall survival was found to be 36.3 months. The disease prognosis and risk stratification are linked to serialized measurement of cardiac biomarkers and free light chains. The treatment of AL amy-

loidosis is mainly based on chemotherapy and autologous hematopoietic stem cell transplantation (ASCT). The use of novel agents (thalidomide, lenalidomide, and bortezomib) alone and in combination with steroids and alkylating agents has shown efficacy and continues to be explored. **Key Messages:** AL amyloidosis is the most common type of systemic amyloidosis in China with increasing morbidity and a high mortality rate. The lack of prospective clinical trials using the current therapies is a challenge for evidence-based decision making concerning the treatment of AL amyloidosis. **Facts from East and West:** (1) AL amyloidosis is the most prevalent type of amyloidosis accounting for 65% of the amyloidosis-diagnosed patients in the UK and for 93% of the amyloidosis-diagnosed patients in China. The predisposition of men over women to develop AL amyloidosis might be higher in China than in Western countries (2:1 vs. 1.3:1). Both in the East and West, incidence increases with age. At the time of diagnosis, edema is twice as frequent and the proportion of renal involvement is higher in Chinese compared to Western patients. (2) Melphalan followed by ASCT is the current

For the prevalence and management of systemic amyloidosis in Western countries, see Nienhuis et al., Kidney Dis 2016;2:10–19.

standard therapy but is restricted to eligible patients. The efficacy and safety of bortezomib combined with dexamethasone were proven in Western patients and recently confirmed in a Chinese cohort. Recent studies in China and the US indicate that bortezomib induction prior to ASCT increases the response rate. Thalidomide and lenalidomide have shown benefit, but toxicity and lack of clinical evidence exclude these agents from first-line therapy. The green tea extract epigallocatechin-3-gallate is under investigation as an inhibitor of AL amyloid formation and a compound that might dissolve amyloid.

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Introduction

In the past decades, economic development, accelerated industrialization, urbanization, and behavioral factors as well as the aging population of China [1] have resulted in a vast change in the disease spectrum. The incidence and associated mortality of chronic, noncommunicable diseases is increasing [2], with examples being chronic kidney disease and tumors [3]. Immunoglobulin amyloid light-chain (AL) amyloidosis is a plasma cell disorder with a low tumor burden, and the kidney is the most commonly affected organ [4]. In recent years, amyloidosis has become the fastest growing disease with more than 100 new cases per year at our center, and the proportion of amyloidosis has increased from 0.56 to 1.5–2% of all renal biopsy cases [5].

Amyloidosis includes a group of diseases characterized by the extracellular deposition of various fibrillary proteins that can autoaggregate in a highly abnormal fibrillary conformation [6]. Mass spectrometry-based proteomics have greatly increased the ability to diagnose and type amyloids; to date, up to 30 amyloidogenic proteins have been identified [7]. AL amyloidosis is the most common form of systemic amyloidosis, with an incidence of 8–10 cases per million person-years in Western countries [8]. This review will focus on the clinical presentation and management of AL amyloidosis in China.

Epidemiology

AL amyloidosis remains a serious challenge for nephrologists because of the multiorgan involvement and high mortality rate. For elderly patients with kidney disease and patients who present with nephrotic syndrome in China, the proportion of amyloidosis patients is higher

than the general kidney disease population [9]. Studies on biopsy-proven renal disease in elderly patients (age ≥ 65 years) demonstrated that 5.99% of patients are diagnosed with amyloidosis, accounting for 16.88% of secondary glomerular diseases [10]. The study also showed that the proportion of patients with amyloidosis increased in parallel with patient age [11].

The data from our center demonstrated that among 456 patients with biopsy-proven systemic amyloidosis, 424 (93%) cases were of the AL type (fig. 1), and 374 cases were of the λ type; other types of systemic amyloidosis included immunoglobulin heavy-chain amyloidosis (3.7%), AA amyloidosis (2.2%), fibrinogen A α -chain amyloidosis (0.7%), apolipoprotein A-I amyloidosis, and genetically variant transthyretin amyloidosis.

Regarding the epidemiological features of AL amyloidosis in China, the data from a cohort of 231 Chinese patients demonstrated that 66.2% were male and 33.8% were female. The mean age was 56 years: 3.7% of the patients were less than 40 years of age, and 7.3% of the patients were older than 70 years of age [12].

Clinical Presentation

The clinical presentation of patients with AL amyloidosis varies from patient to patient. There are some differences between different ethnic groups. The median time from symptom onset to diagnosis was 10 months in the Mayo cohort, 6 months in the Italian cohort, and 7 months in the Chinese cohort. The patients from the Chinese cohort primarily presented with fatigue (40%) and edema (80.6%) at the time of diagnosis followed by orthostatic hypotension (30.2%) and weight loss (27.3%). At the time of diagnosis, 25% of the patients had renal insufficiency. Other clinical manifestations included purpura (12%), recurrent diarrhea (10.6%), congestive heart failure (9.4%), dyspnea (9.8%), and paresthesia (6.1%) [12]. Regarding the Mayo and Italian reports, orthostatic hypotension occurred more frequently in the Italian patients than in the Mayo patients, whereas paresthesia and weight loss were more common in the Mayo patients [13] (fig. 2).

The organ involvement at presentation also shows a difference between the patients from China and Western countries. The Chinese patients had a higher proportion of kidney, heart, and gastrointestinal tract involvement, whereas the Mayo group had a greater proportion of patients with the peripheral nervous system listed as the dominant organ involved. The Italian group had a great-

Fig. 1. Renal pathologic features for AL amyloidosis. **a** Periodic acid-Schiff (PAS) stain shows that amyloid appears as amorphous, hyaline, and PAS weakly positive material. **b** On a trichrome stain, this glomerulus with amyloidosis shows that the amyloid material is pale blue. **c** Congo red shows accumulation of amyloid in the glomerular mesangium, interstitium, and artery, staining red under light microscopic examination. **d** Classic apple-green birefrin-

gence is elicited on polarized light examination of a Congo red stain. **e** An electron microscopic (EM) study reveals the typical ultrastructural appearance of amyloid fibrils, characterized by randomly disposed, nonbranching, 8- to 12-nm-diameter fibrils. **f, g** Extensive accumulation of λ light chains can be clearly identified in the glomerulus and arteriole using immunofluorescence (**f** $\times 200$; **g** $\times 400$).

Fig. 2. The incidence of symptoms at presentation between China and Western countries. CHF = Congestive heart failure; OH = orthostatic hypotension.

er proportion of patients with the kidney and liver listed as the dominant organ involved compared to the Mayo group, but the proportion was still lower than that of the Chinese patients.

Laboratory and Pathologic Features

At the time of diagnosis, nephrotic syndrome was the most prominent clinical manifestation in the Chinese patients. The average proteinuria level was 4.92 ± 2.92 g/24 h, and the serum albumin level was 26.32 ± 6.51 g/l. Additionally, renal tubular injury was relatively common in this group of patients, and urinary N-acetyl- β -D-amino-glucosidase and retinol-binding protein were significantly increased. Furthermore, 25% of the patients had renal dysfunction, and 32.4% of the patients had anemia. The M-proteins noted in patients were primarily λ IgG (36.1%) and λ IgA (18.8%). A total of 32.7% of patients tested negative for serum M-protein.

A series of 186 patients with renal biopsy-proven AL amyloidosis was retrospectively reviewed to reveal an association between clinical and pathological features [14]. Eighty-six percent of the patients were confirmed to have AL- λ , and a monoclonal protein was found in 65.1% of the patients. Glomerular amyloid deposition was detected in all cases, and overt interstitium depositions were found in only 12.1% of patients. The extent of glomerular amyloid deposition was positively correlated with the level of proteinuria. Patients with codeposition of amyloid and immune complexes in glomeruli had higher levels of proteinuria than those without immune complexes. The degree of vascular amyloid deposition was positively correlated with cardiac involvement and hepatic involvement. A high renal amyloid load independently predicted an increased risk for overall death.

Progression and Outcome

The median overall survival time for Chinese patients was 36.3 months [12]. The survival rates at 1, 2, 3, and 5 years were 67, 53, 48, and 35% (fig. 3a), respectively. Multivariate analysis showed that age, liver involvement, cardiac involvement, and the proportion of bone marrow plasma cells were risk factors for patient prognosis. However, special treatment was a protective factor for patient prognosis. The median time that patients remained dialysis free was 50 months. The percentages of patients who remained dialysis free at 1, 2, 3, and 5 years were 78, 69, 62, and 37%, respectively. Multivariate Cox analysis showed that serum creatinine and hypotension were the most important risk factors for renal failure [12].

The patients' clinical characteristics had a great impact on the prognosis. The results showed that patient survival time was significantly shorter in patients with renal dysfunction, hypotension, and cardiac or liver involvement. The median survival time was 42.9 months in patients without renal insufficiency and 11.7 months in patients with renal insufficiency ($p < 0.0001$; fig. 3b). The median survival time in patients with or without hypotension was 15.2 or 48.3 months, respectively ($p < 0.0001$). Similarly, the median survival time in patients without heart or liver involvement was 51.8 or 42.9 months, respectively, but the median survival time was 19.3 months ($p = 0.002$) in patients with heart involvement and 9.2 months ($p < 0.0001$) in patients with liver involvement (fig. 3c, d). However, the survival time in patients receiving special treatment (chemotherapy or stem cell transplantation) was significantly improved. The median survival time was 58.6 months in patients with special treatment and 14.2 months in patients without special treatment ($p < 0.0001$). In addition, the survival time was significantly shorter in patients with multiple organ in-

Fig. 3. Overall survival of all patients and survival of different subgroups according to the clinical characteristics. **a** Overall survival of all patients. **b** Survival difference between patients with and without renal insufficiency. **c** Survival difference between patients with and without heart involvement. **d** Survival difference between patients with and without liver involvement.

involvement. The median survival time was 62.7 months in patients with one involved organ, 21.1 months in patients with two involved organs, and 7.1 months in patients with three involved organs ($p < 0.0001$).

Risk Stratification and Staging

The specific organs and the extent of organ involvement vary considerably in patients with AL amyloidosis; thus, risk stratification is important. Various variables are powerful clinical indicators of poor outcome, including

poor performance status, severe postural hypotension, New York Heart Association (NYHA) functional class 3 or higher, and low systolic blood pressure (<100 mm Hg). Cardiac biomarkers [N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponins] are powerful risk stratification tools, and a cardiac biomarker-based staging system has been adopted [15]. The prognostic models were designed using the threshold values of NT-proBNP and cTnT (NT-proBNP <332 ng/l, cTnT <0.035 ng/ml). Depending on whether the NT-proBNP and troponin levels were both low, were high for only one level, or were both high, the patients were classified as stage I,

II, or III, respectively. Using the cTnT and NT-proBNP model, 33, 30, and 37% of patients were stages I, II, and III, respectively, with median survival times of 26.4, 10.5, and 3.5 months, respectively. The level of free light chains (FLCs) may further refine risk stratification, and they have been incorporated into the Mayo 2012 AL amyloidosis staging system [16]. The low-risk group includes patients without cardiac involvement, low levels of FLCs, and a small plasma cell clone. The very-high-risk group includes patients with very high levels of cardiac biomarkers (stage III and with NT-proBNP >8,500 pg/ml). Nevertheless, most of the patients with AL amyloidosis fall between these two groups [17].

Management of AL Amyloidosis

Although AL amyloidosis remains an incurable disease, much progress has been made in the last decade, and important aspects of clinical care for AL amyloidosis patients are guided by evidence-based treatment recommendations. Recently, the Mayo Clinic and British Society for Hematology published two guidelines on the management of AL amyloidosis. Both guidelines present an extensive review of the literature and were aimed to make recommendations in the context of the best evidence and expert opinion [18, 19]. Current treatment strategies target the clone to decrease the production of the pathologic light chains and thereby stop or reverse organ toxicity and damage. The treatment options for AL amyloidosis include corticosteroids, cytotoxic chemotherapy, high-dose melphalan and autologous hematopoietic stem cell transplantation (ASCT), proteasome inhibitors, and immunomodulatory drugs. Alkylator-based therapy, either standard or high dose with ASCT, has been the mainstay of therapy for decades. The first effective treatment for AL amyloidosis was oral melphalan and prednisone. However, a minority of patients responded, and the median overall survival was only 12–18 months [20]. The introduction of ASCT was a major breakthrough in the treatment of AL amyloidosis [21], and ASCT remains the standard treatment for eligible patients to date. Novel agents such as thalidomide, lenalidomide, or bortezomib broached another treatment avenue for AL amyloidosis.

Consensus criteria to define hematological and organ responses in AL amyloidosis have been published [22]. The evaluation of hematological responses is based on the measurement of serum FLCs: partial hematological response requires the reduction of the dFLC (difference between the involved and uninvolved light chain) by 50%; a

very good partial response (VGPR) requires a dFLC <40 mg/l, and a complete hematological response is defined as a normal FLC ratio. Organ response criteria were modified with the introduction of cardiac biomarkers for the evaluation of cardiac response. A cardiac response is defined as a decrease in NT-proBNP by >30% and 300 pg/ml (if the baseline NT-proBNP is >650 pg/ml) or a ≥ 2 -point decrease in the NYHA class (if baseline NYHA class is III or IV). A renal response is defined as a $\geq 30\%$ decrease in proteinuria or a reduction below 0.5 g/24 h in the absence of renal progression, defined as a >25% decrease in the estimated glomerular filtration rate. A liver response is defined as a 50% decrease in the abnormal alkaline phosphatase value or a decrease in the radiographic liver size by ≥ 2 cm [23].

Proteasome Inhibitors

Proteasome inhibitor-based regimens are a preferred choice due to better response rates and outcomes in phase II studies, and a bortezomib-alkylator steroid combination is preferred where a rapid response is desirable (cardiac involvement, renal impairment, severe hypoalbuminemia, and fluid retention) [19]. Several studies have confirmed that bortezomib combined with dexamethasone (BD) is an active and fast-acting regimen for AL amyloidosis, even in pretreated patients [24, 25]. To further improve the efficacy, this drug can also be used by adding an alkylating agent and dexamethasone. Palladini et al. [26] reported their experience in 230 patients with AL amyloidosis treated with upfront CyBorD (cyclophosphamide, bortezomib, and dexamethasone). In this large series, the overall hematologic response rate was 60%, including a complete response (CR) in 23% of patients. After a median follow-up of 25 months for living patients, cardiac and renal responses were obtained in only 17 and 25% of them, respectively.

We also evaluated the efficacy and safety of BD in the treatment of patients with renal AL amyloidosis. Seventy-two patients who were newly diagnosed with AL amyloidosis and renal (100%), cardiac (72.2%), liver (19.4%), or nervous system (9.7%) involvement underwent a median of 2 (1–6) cycles of BD treatment. A hematologic response was achieved in 75% of patients within a median time of 2 months, including 44.5% CRs. A renal response was achieved in 50% of the patients after 1 year and in 60% after 2 years, and a cardiac response was documented in 40.4% of patients after 1 year and in 45.5% after 2 years. The median time of progression-free survival was 45 months, and the estimated overall survival rates at 12 and 24 months were 83.0 and 75.8%, respectively [27].

Immunomodulatory Agents

The efficacy of immunomodulatory agents in multiple myeloma provided another promising treatment option for AL amyloidosis. Both lenalidomide and thalidomide are not recommended as first-line therapy except perhaps for patients with an excellent performance status. Although both thalidomide and lenalidomide are available for patients with AL amyloidosis in China, the clinical data regarding thalidomide or lenalidomide-based regimens for AL amyloidosis are rare.

Thalidomide, the first of these agents, was effective with hematologic response rates of 48%, a CR of 19%, and an organ response of 26% when combined with dexamethasone, but treatment-related toxicity was frequent, and the agent was poorly tolerated [28]. Lenalidomide is a second-generation immunomodulatory agent with greater anti-myeloma efficacy and a favorable toxicity profile. When combined with cyclophosphamide and dexamethasone, the hematologic response rate was 60%; in those receiving at least 4 cycles, the response rate was 87%. The median overall survival time was 37.8 months [29].

Autologous Stem Cell Transplantation

ASCT has been successful in inducing complete hematologic remissions and prolonging survival in patients with multiple myeloma. Therefore, it was logical to apply this approach to the treatment of AL amyloidosis. ASCT is the preferred first-line treatment for selected patients up to 65–70 years of age with preserved organ function. To be transplant eligible, the following criteria should be met: a physiologic age 70 years or younger; a performance score of 2 or less; a troponin T level <0.06 ng/ml; creatinine clearance of at least 30 ml/min (unless undergoing long-term dialysis); NYHA class I/II; no more than 2 major organs significantly involved (liver, heart, kidney, or autonomic nerve), and low-level plasma cell infiltration in the bone marrow at the time of transplant [18].

The Boston Amyloidosis Center reported long-term outcomes of 607 subjects with AL amyloidosis undergoing ASCT. Of these subjects, 53% had cardiac involvement, and 41% had multiorgan involvement. The treatment-related mortality (TRM) was 9%, and 80% of the deaths were associated with cardiac involvement. The hematologic CR was 34% by intention-to-treat analysis. The hematologic CR was 45% for those who received 200 mg/m² of melphalan compared with 33% for those who received 100–140 mg/m² of melphalan. The median overall survival was 6.7 years. The median overall survival was significantly better for those who achieved a hematologic

CR, for those without cardiac involvement, and for those with less than 2 organ systems involved [30]. TRM was the largest obstacle for AL amyloidosis treatment with ASCT in the early stage. The TRM was 12–13% at the major center conducting ASCT [31]; patients with advanced organ damage were exposed to an unacceptably high risk (more than 40%) of TRM [32]. In recent years, refining the patient selection has allowed ASCT to be performed safely, but the eligibility of patients for ASCT has decreased outside of centers with extensive transplant experience [33].

BD Induction before ASCT

To further improve the response rate in patients with AL amyloidosis, we designed a single-center, prospective, randomized controlled trial to evaluate BD for induction chemotherapy prior to ASCT. Fifty-six patients newly diagnosed with AL amyloidosis were enrolled in this study; 28 patients were assigned to each arm. A higher rate of complete remission in the BD + ASCT arm was found at both 12 and 24 months (67.9 and 70%, respectively) than with the ASCT-alone therapy (35.7 and 35%, respectively; $p = 0.03$). After a median follow-up of 28 months, the survival rates 24 months after treatment start were 95.0% in the BD + ASCT group and 69.4% in the ASCT-alone group ($p = 0.03$). The results suggest that induction therapy with BD followed by ASCT is an effective and tolerable regimen for treating patients with AL amyloidosis [34]. This protocol can significantly improve both the hematological and organ response rates, and the risk of the BD followed by ASCT regimen is apparently comparable to that of ASCT.

Sanchorawala et al. [35] also report their experience with induction therapy plus bortezomib followed by bortezomib/high-dose melphalan and stem cell transplantation for AL amyloidosis. Thirty-five patients were enrolled in that study. Hematologic responses were achieved in 100% of the 27 assessable patients (63% CR, 37% with a VGPR) who completed the planned treatment. The hematologic responses occurred in 77% of patients (49% with a CR, 29% with a VGPR). With a median follow-up of 36 months, the median overall survival and progression-free survival were not reached. It seems that the combined bortezomib plus ASCT regimen yielded a high rate of hematologic responses in patients with AL amyloidosis. In a retrospective study, 28 consecutive patients with de novo AL amyloidosis deemed ineligible at initial presentation received bortezomib-based treatment. Hematological and organ responses induced with bortezomib-based therapy enabled 8 (33%) of the initial-

ly transplant-ineligible patients to undergo ASCT, including 4 patients with cardiac stage III or IV disease [36]. These data suggest that bortezomib-based induction followed by ASCT is also a viable therapeutic strategy for transplant-ineligible AL amyloidosis patients.

Conclusion

AL amyloidosis remains a challenge for physicians with increasing morbidity and a high mortality rate. The treatment of AL amyloidosis is mainly based on chemo-

therapy and ASCT, but the evidence from clinical trials of AL amyloidosis treatment from China remains limited. Therapies targeting amyloid deposits and the amyloidogenic process are new approaches that will shed light on integrative therapy for patients with AL amyloidosis.

Conflict of Interest Statement

All authors declare that they have no competing interests.

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