Original Study

Clinical Characteristics and Treatment Outcome of Chinese Patients With Systemic Amyloid Light-Chain Amyloidosis: A Retrospective Single-Center Analysis

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Abstract

A retrospective analysis of 123 amyloid light-chain amyloidosis patients in a single center of China found that compared to other studies abroad, patients were younger and more had organ involvement. Hypoalbuminemia, renal failure, and heart involvement were important to survival. Additionally, rapid treatment response time (within 3 months) significantly improved prognosis.

Background: Amyloid light-chain (AL) amyloidosis is a disease caused by tissue deposition of light-chain proteins in vital organs that results in progressive organ damage. We analyzed the clinical characteristics of 123 AL amyloidosis patients and performed an overall survival (OS) analysis to identify critical baseline factors. **Patients and Methods:** Patients (median age, 54 years) were diagnosed with organ involvement of kidney (98.4%), gastrointestinal (73%), cardiac (56%), liver (13%), or nervous system (10%), and multiorgan involvement was observed in 91% of patients. Treatment regimens of transplantation, bortezomib plus dexamethasone, melphalan plus dexamethasone, and prednisone-based regimens or no treatment resulted in 3-year OS rates of 72%, 60%, 55%, and 41%, respectively. **Results:** Median OS was 38 months and was affected by age (≥ 65 years), hypoalbuminemia, renal failure, heart involvement, and organ response time (within 3 months). Multivariate analysis indicated that these were independent prognostic factors on OS except for age. **Conclusion:** The AL amyloidosis patients in this study presented somewhat different features and outcomes compared to others, with younger age and higher rates of organ involvement.

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Introduction

Amyloid light-chain (AL) amyloidosis is a systemic disease with deposition of misfolded protein fibrils in various tissues and organs. The amorphous amyloid fibrils are derived from monoclonal immunoglobulin light chains, which are produced by an underlying clonal plasma cell dyscrasia.[1] AL amyloidosis is an uncommon disease, affecting 5 to 12 people per million per year.[2] The symptoms are often nonspecific, leading to delays in diagnosis and advanced organ dysfunction when treatment is initiated. The overall prognosis of this disease is poor because accumulation of pathogenic amyloid deposits in vital tissues or organs such as the heart, kidneys, liver, gastrointestinal tract, or nerves can cause substantial morbidity and often leads to rapidly progressive organ failure and death.[3,4]

Because the mechanism of the formation of amyloid fibril and organ involvement is still unclear, there is no specific therapeutic option available targeting amyloidosis. The main and direct treatment of AL amyloidosis is to suppress malignant plasma cell clones, as in multiple myeloma.[5] Intensive chemotherapy regimens, including high-dose melphalan with autologous peripheral blood stem cell transplantation (HDM/SCT) and the combination of melphalan with dexamethasone (MD),[6-8] have been provided to AL amyloidosis patients, resulting in significantly improved prognosis.[9] Use of novel agents such as bortezomib and immunomodulatory drugs have also exhibited promising outcomes.[10,11] However, the efficacy of the various treatments is difficult to define and somewhat

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controversial.[12] Furthermore, prognosis depend on multiple factors, such as patient age, physical conditions, and more important the severity of organ involvement and the type and number of organs already affected. Accumulation of documented clinical data from larger patient populations of different geographical regions will be beneficial for better diagnosis, prognosis evaluation, and formulating treatment regimens at treatment centers.

Currently, relevant studies of AL amyloidosis are mainly concentrated in more advanced countries in Europe and the United States. Reports on the diagnosis and therapeutics of AL amyloidosis in disadvantaged developing countries in Asia, including China, are scarce. We thus performed a retrospective analysis of 123 AL amyloidosis patients from a single center in China. We focused on clinical manifestation, disease response, and treatment outcome of AL amyloidosis. The results directly benefit current practice of AL amyloidosis diagnosis and therapies for favorable patient outcomes. Additionally the study contributes to the enlargement of existing data pool for future meta-analysis.

Materials and Methods

Ethical Statement

This study was approved by the Clinical Research Ethics Committee of Jinling Hospital, Nanjing, China. Written informed consent was waived by the ethics committee.

Patients and Diagnosis

The reported patient population consisted of 123 patients with AL amyloidosis admitted to the Jinling Hospital in Nanjing, China, between 2000 and 2010. AL amyloidosis was diagnosed and confirmed by biopsy in combination with clinical signs of organ involvement according to the Consensus Criteria.[13] Amyloidosis of AL subtype was determined by the presence of Congo Red–positive fibril deposition and apple-green birefringence viewed under polarized light with the documentation of a monoclonal protein by biopsy. Immunohistochemistry was used to confirm either κ or λ light-chain specificity of the fibrils. Evidence of clonality was required, such as monoclonal protein presences in serum or urine, light-chain excess of serum-free light-chain analysis, or clonal plasma cell population within the bone marrow. Patients who met the 3 criteria of multiple myeloma diagnosis were excluded: clonal bone marrow plasma cells $\geq$ 10%, presence of serum and/or urinary monoclonal proteins, and evidence of end-organ damage that can be attributed to an underlying plasma cell proliferative disorder. Other types of amyloidosis, such as secondary and familial amyloidosis, were also excluded. Serum creatinine level beyond 1.2 mg/dL was defined as renal failure, and the definition of hypoalbuminemia was below 30 g/L. A hematologic complete response was defined as having no evidence of clonal disease by electrophoresis and immunofixation in serum or urine with normal free light-chain levels and ratio. The difference between involved and uninvolved free light-chain serum level (dFLC) responses were evaluated, with very good partial response defined as posttreatment dFLC level $<$ 40 mg/L and partial response by a 50% drop in dFLC serum level.[14]

Treatments

Treatment options included HDM/SCT (melphalan dose level, 140-200 mg/m^2), bortezomib exposure in combination with

Table 1 Demographics, Clinical Characteristics, and Treatment of 123 Patients

Characteristic	Variable	Value
Gender (male/female), n (%)		83/40 (67/33)
Age (years), median (range)		54 (34-82)
Time from onset of symptom to diagnosis (months), median (range)		7 (0.5-96)
Biopsy site	Renal	114 (86.3)
	Gastrointestinal	58 (47.2)
	Bone marrow	11 (8.9)
	Skin	10 (8.1)
	Hepatic	1 (0.8)
Isotype	κ/λ	14/86 (14/86)
Heavy chain	IgG	37 (41.5)
	IgA	14 (15.7)
	IgM	1 (1.1)
	LCD (κ/λ)	32 (8/24) (35.9)
	Nonsecretory	5 (5.6)
Serum free light-chain ratio	Abnormal	26 (26/26,100%)
	Increased κ	6 (6/26, 23.1%)
	Increased λ	20 (20/26, 76.9%)
Organ involvement	Renal	121 (98.4)
	Gastrointestinal	89 (72.9)
	Heart	68 (55.7)
	Soft tissue	23 (18.8)
	Liver	16 (13.1)
	Neuropathy	12 (9.8)
	Bone marrow	6 (4.9)
	Lung	2 (3.6)
No. of organs involved	1	11 (8.9)
	2	46 (37.4)
	3 or more	66 (53.7)
BM plasma cell	$\leq$5%	106 (86.2)
	$>$5%	17 (13.8)
HB (g/L), median (range)		122 (57-175)
Serum albumin	$\geq$35 g/L	14 (11.8)
	30-35 g/L	16 (13.8)
	25-30 g/L	31 (26.1)
	$<$25 g/L	58 (48.7)
Treatment	HDM/SCT	15 (12.2)
	VD	23 (18.7)
	MD	33 (26.8)
	Prednisone based	42 (34.1)
	Other (including no treatment)	10 (8.1)
IVS $\geq$15 mm		21 (17.1)
LVEF $<$45%		17 (17/98, 17.3%)
Proteinuria (g/24 hours) (range)		4.81 (0.1-25.79)
	$>$1 g/day	109 (88.6)
	$>$3.5 g/day	80 (65.0)
Creatinine	$>$1.2 mg/dL	35 (28.5)
ALP greater than normal value		15 (12.2)