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Review Article

The Diagnosis and Evolving Treatment Landscape of Systemic Light Chain Amyloidosis: A State-of-the-art Review

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Abstract

Systemic light chain (AL) amyloidosis is a rare and potentially fatal disease characterized by the abnormal deposition of homogeneous, amorphous amyloid proteins in tissues and organs. This deposition leads to varying degrees of structural and functional abnormalities, ultimately causing organ dysfunction and failure. The disease often involves multiple systems and organs, including the heart, kidneys, gastrointestinal tract, liver, and nervous system, with cardiac and renal involvement being the most common. Due to its rarity, multisystem involvement, and rapid progression, a comprehensive summary of the diagnosis and treatment of AL amyloidosis is crucial for guiding clinical practice and advancing research in this field. This article reviews the progress in diagnosis and discusses future treatment of AL amyloidosis, aiming to provide expanded options for clinical practice.

Introduction

Amyloidosis is a disease of abnormal protein folding, in which the light chain of monoclonal immunoglobulin is transformed from its soluble functional state to the highly organized amyloid protein, which is deposited in tissues and organs, resulting in tissue structure destruction and organ dysfunction.[1–3] The disease can affect multiple organ systems throughout the body, such as the heart, kidneys, gastrointestinal tract, nervous system, and liver, among which heart and kidney damage are most common.[4,5] With the aging of the population, the incidence of systemic light chain (AL) amyloidosis is increasing year by year. According to foreign statistics, the incidence is about 10 per million people per year.[6] Most identified patients are usually diagnosed at an advanced stage, and 25 percent die within six months of diagnosis.[7] Especially when the heart is involved, the disease often progresses rapidly, with a high risk of death within months. Amyloidosis is classified into systemic amyloidosis and focal amyloidosis based on the affected area, and further categorized by precursor protein types, including AL amyloidosis, transthyretin type, and serum amyloid A type, among more than thirty types of amyloidosis. Among these, AL amyloidosis is the most common type of systemic amyloidosis.[8] AL amyloidosis is often associated with plasma cell disorders (such as multiple myeloma (MM) or monoclonal gammopathy of unknown significance), but it can also occur independently. Due to its highly heterogeneous clinical presentation and atypical early symptoms, the disease is prone to misdiagnosis or missed diagnosis, leading to poor prognosis. In recent years, with advancements in molecular diagnostic techniques and the development of targeted therapies, the diagnosis and treatment of AL amyloidosis have significantly improved. This article focuses on the diagnosis and treatment progress of AL amyloidosis, in order to provide a reference for its clinical diagnosis and treatment.

Mechanism and risk factors of AL amyloidosis

Occurrence mechanism

The pathogenesis of AL amyloidosis is complex, involving abnormal protein folding, aggregation, and deposition. AL amyloidosis is associated with the abnormal proliferation of monoclonal plasma cells in the bone marrow and excessive secretion of immunoglobulin light chains.[9] These light chains, due to genetic mutations or abnormal post-translational modifications, exhibit structural instability and are prone to misfolding, forming β-sheet layers. Misfolded light chains expose hydrophobic regions, which self-assemble into insoluble amyloid fibrils through the β-sheet layer structure. These fibrils deposit in the extracellular matrix, exerting

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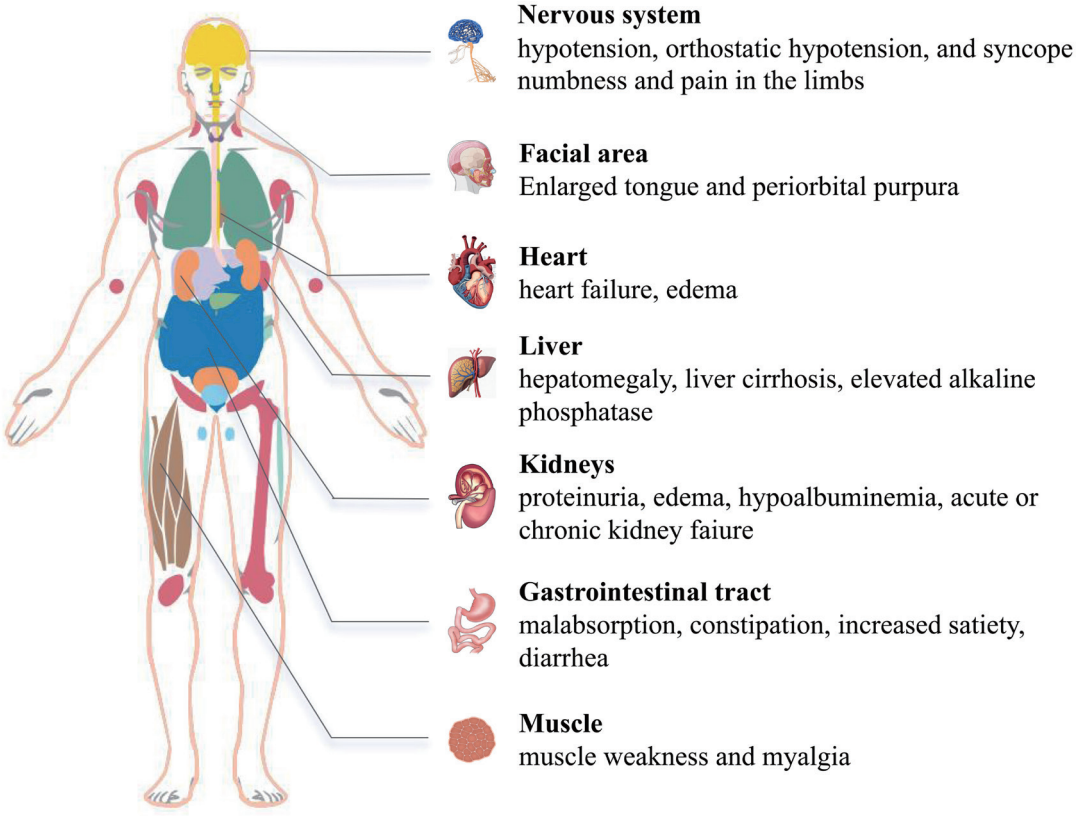

Fig. 1. Clinical manifestation of systemic light chain (AL) amyloidosis. This figure summarizes the important clinical features of AL amyloidosis, including the main clinical manifestations of the heart, kidneys, liver, gastrointestinal tract, autonomic and peripheral nervous system, and soft tissue.

pressure on normal tissue structures and causing direct toxicity. They interact with cell membranes, producing reactive oxygen species and triggering oxidative stress responses. Simultaneously, they activate macrophages and the complement system, leading to chronic inflammation and progressive organ dysfunction.[1]

Risk factors

AL amyloidosis is associated with a number of factors, among which age, other diseases, and genetics are related risk factors.

1. *Age:* AL amyloidosis is more common in middle-aged and elderly people, with an average age of 56 years, most commonly in those aged 50–59 years. The higher the age, the worse the treatment effect. Age is an independent factor influencing survival prognosis, and increasing age increases the risk of death.[10]
2. *Other diseases:* Studies have shown that patients with monoclonal gammopathy of undetermined significance may be at increased risk of developing AL amyloidosis. For patients with these conditions, regular follow-up monitoring and evaluation for signs of AL amyloidosis are important.[11]

Clinical manifestations and diagnostic methods of AL amyloidosis

Clinical manifestation

Amyloidosis is a systemic disease that can affect all organs throughout the body. Its symptoms and signs depend on the affected organs and systems, most commonly involving the heart and kidneys. Common clinical manifestations include edema, proteinuria, hematuria, heart failure, hepatosplenomegaly, diarrhea, and skin itching. "Enlarged tongue and periorbital purpura" are highly specific clinical features of amyloidosis, but they occur in only 15% of patients.[12]

Amyloid deposition can affect any organ system, with the initial symptoms primarily driven by organ dysfunction caused by amyloid deposition. Cardiac amyloidosis manifests as signs and symptoms of heart failure, and cardiologists typically raise the initial suspicion during echocardiographic evaluation, which suggests infiltrative cardiomyopathy.[13] For patients with kidney involvement, the main clinical manifestations include proteinuria, edema, hypoalbuminemia, and acute or chronic renal insufficiency.[14] Other organs may be affected, including the liver (such as hepatomegaly, liver cirrhosis, and elevated alkaline phosphatase) and gastrointestinal tract (such as malabsorption, constipation, increased satiety, and diarrhea), along with other manifestations like musculoskeletal disorders (such as muscle weakness and myalgia), autonomic nervous system involvement (such as hypotension, orthostatic hypotension, and syncope), and peripheral nerve involvement (such as numbness and pain in the limbs). These symptoms are often non-specific and require a high degree of suspicion (Fig. 1).

Diagnostic method

Biopsy and immunohistochemistry

Biopsy combined with immunohistochemical testing is a critical step in diagnosing AL amyloidosis. Tissue samples are obtained

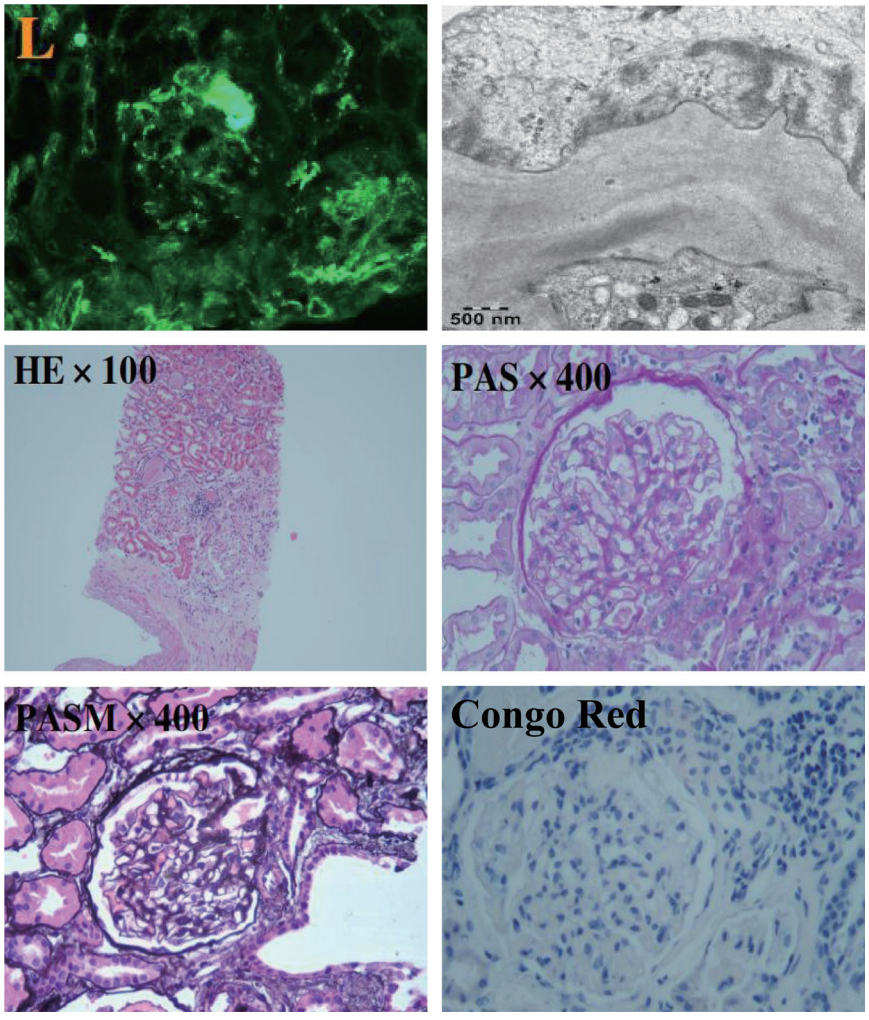

Fig. 2. Kidney biopsy pathological picture of systemic light chain (AL) amyloidosis. This image includes immunofluorescence, ultrastructure, and histological examination (HE, PAS, PASM, Masson staining) (donated by Professor Geng Jian). (a) Immunofluorescence staining (the letter "L" represents the immunofluorescence λ light chain staining showing a large accumulation of amyloid material), (b) Electron microscopy observations, (c) HE staining, (d) PAS staining, (e) PASM staining, (f) Congo red staining. HE, hematoxylin and eosin staining; PAS, periodic acid–Schiff; PASM, periodic acid–Schiff methenamine.

through biopsy, and Congo red staining is used to detect the presence of amyloid protein. The type of amyloid protein is then determined using immunohistochemistry or mass spectrometry. Once AL amyloidosis is suspected, biopsy must show Congo red-positive amorphous deposits under polarizing light microscopy, accompanied by apple-green birefringence (Fig. 2).[15] Common biopsy sites include subcutaneous fat, lip gland, and affected organs. Peripheral tissue biopsy is fast, simple, and safe, but its sensitivity is not as high as that of target organs, while organ biopsy is more complex and has a higher risk of bleeding.[8] Bone marrow biopsy is usually the most common source of tissue specimen evaluation, but its biopsy positive rate is only 50–60%.[16] Fine needle aspiration of abdominal fat amyloid deposition is positive in approximately 70% to 75% of patients with AL amyloidosis, and combining abdominal fat and bone marrow biopsy specimens yields positive results in 85% of patients.[17]

Serum and urine tests

In addition to biopsies, serum and urine tests are also crucial in the diagnosis of AL amyloidosis. Studies have shown that serum immunofixation has a moderate sensitivity of 50% to 60% for AL amyloidosis; however, when combined with urinary immunofixation, the sensitivity can be increased.[18] In addition, serum free light chain (sFLC) testing has 76.0% sensitivity for the diagnosis of AL amyloidosis.[19] The sensitivity of the combined test using sFLC and serum immunofixation/urinary immunofixation is 97% to 100%.[20,21] Additionally, biomarkers such as troponin, N-terminal precursor brain natriuretic peptide (NT-proBNP), and 24-h urine protein measurement also have potential value in diagnosis and prognosis assessment.

Imaging studies

Imaging plays a crucial role in the diagnosis and evaluation of AL amyloidosis. Techniques such as echocardiography, myocardial perfusion imaging, and cardiac magnetic resonance imaging can be used to assess cardiac involvement. Cardiac magnetic resonance imaging is more sensitive for detecting cardiac damage in subclinical patients with AL amyloidosis.[22] In addition, 18F-Flor-

Table 1. Starch-like degeneration staging model

Model	Cardiac troponin T	Cardiac troponin I	High-sensitivity cardiac troponin T	NT-proBNP	B-type natriuretic peptide
Mayo 2004 model	≥0.035 mcg/L	≥0.1 mcg/L	≥50 ng/L	≥332 ng/L	≥81 ng/L
Modification of Mayo 2004 model	≥0.035 mcg/L	≥0.1 mcg/L	≥50 ng/L	≥332 ng/L ≥8,500 ng/L	≥81 ng/L ≥700 ng/L
Mayo 2012 model	≥0.025 mcg/L	–	≥40 ng/L	≥1,800 ng/L	≥400 ng/L
Mayo Autologous Stem Cell Transplantation troponin risk marker	≥0.06 mcg/L	–	≥75 ng/L	–	–
Boston University Staging		≥0.1 ng/mL		–	≥81 ng/L

betaben positron emission tomography/computed tomography has important clinical value and good application prospects in the differentiation of AL cardiac amyloidosis.[23]

Phenomenon of disease staging and risk stratification in AL amyloidosis

The staging system currently used for risk stratification and prognosis utilizes biomarkers of plasma cell tumor burden as well as cardiac and renal involvement (Table 1).[24]

Cardiac involvement is a major prognostic factor for survival. The Mayo 2012 staging system is one of the most widely used tools for risk stratification in AL amyloidosis. This system divides patients into four prognostic stages based on three risk factors: cardiac troponin T (≥0.025 μg/L), NT-proBNP (≥1,800 ng/L), and free light chain (FLC) difference (≥180 mg/L). It comprehensively evaluates disease status and survival prognosis.[25]

Treatment strategies and prognosis analysis of AL amyloidosis

Treatment strategy

For newly diagnosed patients with AL amyloidosis, accurate risk stratification is crucial for formulating treatment strategies. The primary goal of treatment is to reduce the level of monoclonal immunoglobulin light chains in the body, prevent further deposition of amyloid proteins in vital organs, and alleviate or reverse organ dysfunction caused by amyloid protein deposition. Among initially diagnosed patients with AL amyloidosis, about 20% are suitable for autologous hematopoietic stem cell transplantation (ASCT), and some patients, after effective induction therapy in the early stage, can also undergo ASCT later. Multiple clinical studies have shown that among newly diagnosed patients with AL amyloidosis who receive induction therapy based on bortezomib, 84% achieve a hematological response after ASCT treatment (with a very good partial response (VGPR) rate of 33% and a complete response (CR) rate of 39%). After "consolidation" treatment with a bortezomib-based regimen following ASCT, the CR rate can increase to about 60%, and the minimal residual disease (MRD) negative rate is approximately 40%.[26] The overall survival rate of patients with newly diagnosed AL amyloidosis who achieved CR after ASCT treatment was over 50% at 15 years.[27]

Patients who do not meet the ASCT criteria are recommended to receive a bortezomib-based chemotherapy regimen as early as possible, usually in combination with cyclophosphamide and dexamethasone (CyBorD). Clinical studies have shown that adding daratumumab to CyBorD-based therapy as a combination induction can lead to deeper hematological responses, improved organ function, and better survival outcomes compared to using CyBorD alone. Seventy-eight percent of patients achieve VGPR or better hematological responses, and approximately 50% to 55% of patients show organ responses after 18 months of treatment. Additionally, the combination of daratumumab with bortezomib, cyclophosphamide, and dexamethasone is beneficial for translocation (11;14) patients.[28]

For patients with AL amyloidosis who fail to achieve a deep hematological response through first-line chemotherapy, second-line treatment may be necessary. Currently, commonly used second-line treatments include pomalidomide, ixazomib, and bendamustine. However, the proportion of patients achieving a hematological response of VGPR or better with these drugs is not high: 18% to 38% for pomalidomide, 36% to 43% for ixazomib, and 23% for bendamustine.[29] Retrospective studies have shown that the combination of daratumumab, bortezomib, and dexamethasone is effective as a second-line treatment for AL amyloidosis, and in relapsed patients, the response rate is close to that of Dara-VCD in front-line treatment.[30]

Teclistamab is a bispecific antibody targeting B cell maturation antigen (BCMA) and T cell CD3 receptor. The overall response rate of phase 1–2 studies in patients with MM was 63%, with 39.4% of patients achieving complete remission or better and 26.7% achieving MRD negativity.[31] Recently, it has been approved by the U.S. Food and Drug Administration for the treatment of relapsed or refractory MM. Traditionally, the treatment of AL amyloidosis has often referenced MM therapies. People have started to consider the efficacy and safety of teclistamab in AL amyloidosis. A retrospective study showed that 88% of patients with relapsed or refractory AL amyloidosis achieved VGPR with teclistamab, including 41% in CR status, but no cardiac or renal toxicity was recorded.[32]

While initial treatment with daratumumab-based therapies represents a significant advance in the treatment of AL amyloidosis, nearly half of patients do not achieve CR (47%), and there is no guarantee of organ response.[28] Chimeric antigen receptor T cell therapy is a novel therapeutic strategy mediated by genetic engineering. Similar to MM, BCMA is highly expressed in amyloid-producing plasma cells and is retained during relapse.[33] A phase Ia/b study (NCT04720313) of a novel anti-BCMA chimeric antigen receptor T cell therapy developed at Hadassah Medical Center has demonstrated for the first time the safety and efficacy of this strategy in treating advanced, recurrent, or refractory AL amyloidosis patients.[34]

Due to the involvement of multiple organ systems in AL amyloidosis, despite hematological responses during treatment, progressive organ failure may still occur. In patients with kidney involvement, this can ultimately lead to end-stage renal disease, and isolated kidney damage may also be present. A multicenter retro-

spective study included 237 patients with AL amyloidosis who received kidney transplants between 1987 and 2020, with a median follow-up of 8.5 years. The median overall survival after kidney transplantation was 8.6 years, and it was found that the median overall survival time for patients with AL amyloidosis was better than that for non-amyloidosis kidney transplant patients.[35] Patients whose hematological response reached CR or VGPR had better survival, median graft survival, and lower graft recurrence than those without a hematological response.[35,36] However, there is currently no unified standard for determining which AL amyloidosis patients are more suitable for kidney transplantation. Studies suggest that patients who receive chemotherapy before kidney transplantation and achieve a hematological response of CR or VGPR have better outcomes. For AL amyloidosis patients who progress to advanced heart failure, these patients may benefit from heart transplantation.[37] Kraus *et al*.[25] reported 115 patients with cardiac amyloidosis who received heart transplants during two different periods (1987–2007 and 2008–2020). The median overall survival in both periods was 6.3 years, with the survival period for patients who received transplants between 2008–2020 (9.7 years) being significantly higher than that for those between 1987–2007 (1.8 years). Therefore, heart transplantation may be the ultimate treatment option for myocardial amyloidosis, but it requires thorough evaluation.

Therefore, the treatment goal for patients with AL amyloidosis is to prevent disease progression, achieve the best hematological response possible, strive for organ function reversal, and prolong survival time. With the continuous development of new drugs and the improvement of treatment standardization, the survival and prognosis of patients with AL amyloidosis have been significantly improved.

Prognosis assessment

In recent years, with advances in diagnostic and treatment techniques, the prognosis of patients with AL amyloidosis has improved, but overall survival remains short. The main determinant of amyloidosis outcomes is the degree of cardiac involvement.[24] The Mayo Clinic uses NT-proBNP, BNP, and cardiac troponin not only as markers for the staging of amyloidosis, but also to assess prognosis.[38] Therefore, during the diagnosis and treatment process, it is necessary to closely monitor cardiac function indicators and make early judgments on heart involvement. For patients with concurrent heart failure, active supportive therapy should be provided. In addition to myocardial markers, there is a strong correlation between the degree of reduction in FLCs of amyloid protein and improvements in survival rates. Changes in FLC and NT-proBNP can predict survival rates up to three months after the start of treatment.[39] However, for patients with renal insufficiency, the accumulation of serum FLC may limit the level of sFLC. Therefore, the FLC κ/λ ratio is used for disease diagnosis, rather than FLC levels alone, and the difference between affected and unaffected FLC is introduced as a parameter for monitoring the disease.[40] In addition, bone marrow plasma cells are associated with a poor prognosis in 20% or more of patients with AL amyloidosis.[15] A recent retrospective multicenter cohort study has shown that the depth of 24-h proteinuria reduction can inform the risk and survival of kidney replacement therapy and better assess the effectiveness of treatment.[41]

Another important prognostic factor for AL amyloidosis is the depth of response to treatment. Current evidence suggests that patients with deeper remission have longer recurrence-free and overall survival times. However, there is no consensus on methods for evaluating MRD. Studies using flow cytometry to assess MRD in patients show higher organ remission rates, progression-free survival, and very low hematological relapse in MRD-negative AL amyloidosis patients.[42,43] Comparing the MRD-negative and MRD-positive groups, 88% and 64% (P = 0.06) of patients had kidney responses, 75% and 59% (P = 0.45) had heart responses, and 90% and 75% (P = 0.20) had responses in any organ. These data suggest that there may be a correlation between a higher probability of MRD negativity and organ responses after AL amyloidosis treatment.[44] A meta-analysis incorporating nine studies involving 451 patients found that in AL amyloidosis, MRD negativity was associated with higher cardiac or renal response rates and indicated better progression-free survival during follow-up; however, the correlation between overall survival and MRD status was not significant.[42] Therefore, it is unclear whether the treatment of AL amyloidosis should aim for MRD negativity, or whether patients with MRD positivity require more aggressive chemotherapy regimens or ASCT. Whether MRD can guide the assessment of prognosis and adjustment of further treatment in AL amyloidosis warrants further research.

Perspectives

With the advancement of experimental techniques, our research on the pathogenesis of type AL amyloidosis has made significant progress. In terms of diagnosis, new diagnostic and therapeutic technologies are emerging, and the discovery of various novel markers is further guiding clinical prognosis assessment. Immunotherapy represents the greatest recent progress in treating type AL amyloidosis. Immune therapies, represented by DARA, have shown promising clinical outcomes in treating type AL amyloidosis, significantly improving patient outcomes. Additionally, emerging treatments such as gene therapy and cell therapy also warrant attention and exploration. Due to the rarity of type AL amyloidosis, the number of cases at individual centers is limited, leading to significant heterogeneity in clinical presentation and prognosis among patients with type AL amyloidosis. Large-scale multicenter studies are needed to increase sample sizes, which will help more accurately evaluate different diagnostic and treatment strategies, ultimately leading to personalized treatment plans.

Conclusions

Significant progress has been made in the diagnosis and treatment of AL disease. Accurate diagnosis and evaluation of AL amyloidosis are essential prerequisites for effective therapy. The gold standard diagnostic approach emphasizes Congo red staining from tissue biopsies combined with mass spectrometry analysis, while imaging techniques are crucial for precisely assessing involvement of vital organs such as the heart. With the continuous emergence of new drugs, treatment strategies have evolved from traditional chemotherapy combined with autologous stem cell transplantation to a comprehensive era of immunotherapy centered on daratumumab. This targets rapid and deep clearance of pathogenic light chains in circulation to reverse organ damage. The prognosis of this disease is directly related to the depth and speed of hematologic remission and the achievement of organ response. In the future, more cutting-edge drugs targeting amyloid deposition itself, more refined risk stratification, and exploration of refractory cases will be key directions to further improve patients' long-term quality of life.

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Conflict of interest

One of the authors, Fuming Zi, has been an editorial board member of the *Oncology Advances* journal since August 2023.

Author contributions

Study concept, study design (FZ), and drafting of the manuscript (TY). Both authors have approved the final version and publication of the manuscript.

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