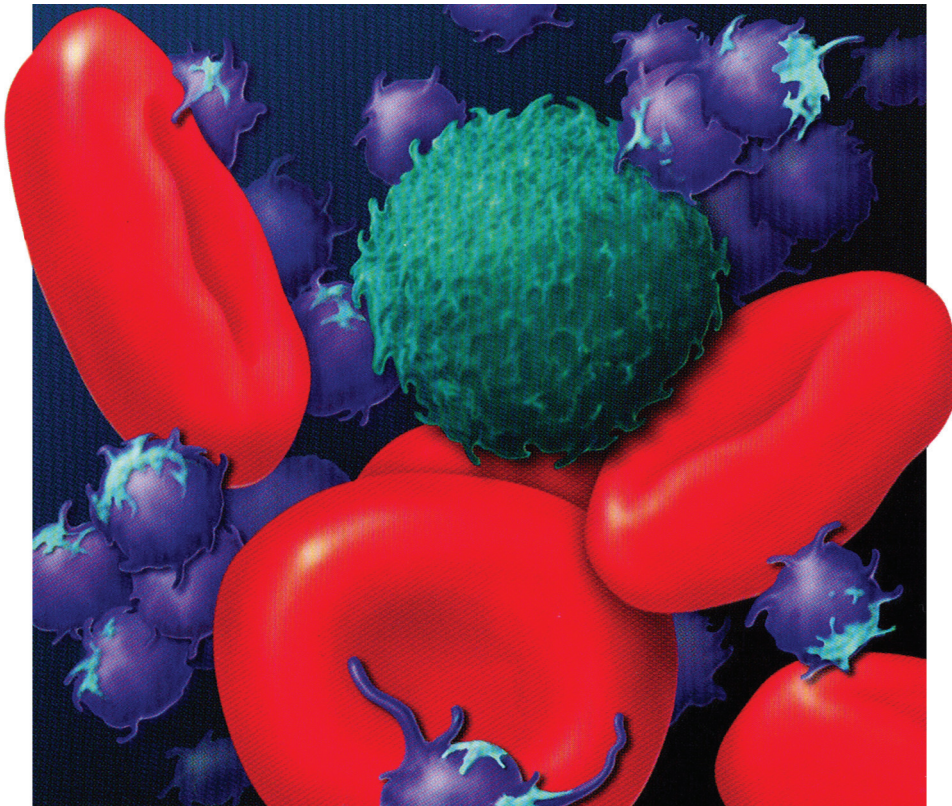


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Diagnosis and Management of Immunoglobulin Light Chain Amyloidosis

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HEMATOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Hematology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

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Diagnosis and Management of Immunoglobulin Light Chain Amyloidosis

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Table of Contents

Introduction	2
Etiology and Epidemiology	2
Clinical Features and Presentation	2
Diagnostic Evaluation	3
Management	4
Conclusion	9
Board Review Questions	9
References	9

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Diagnosis and Management of Immunoglobulin Light Chain Amyloidosis

Jason S. Starr, DO, and Taimur Sher, MD

INTRODUCTION

The term *amyloidosis* refers to a fascinating group of disorders that share a common pathogenesis of extracellular deposition of amyloid material. Fundamentally, it is a disorder of the secondary structure of select proteins whereby the amyloidogenic proteins are misfolded into a β -pleated sheet configuration, resulting in the formation of insoluble extracellular amyloid fibrils. The amyloid fibrils appear as amorphous eosinophilic material when hematoxylin and eosin-stained tissue is examined under light microscope. Electron microscopy reveals remarkable similarity between the amyloid fibrils derived from different precursor proteins in that they range from 7.5 to 10 nm in diameter. This ultrastructural similarity is the underlying basis for the characteristic red-green birefringence with Congo red staining observed under polarized microscopy, the pathological hallmark of the disease.¹

Despite the profound similarity in the biochemical composition of the amyloid, it is the nature and source of the precursor (amyloidogenic) protein that separate this homogeneous pathological entity into very distinct clinical disorders belonging to inflammatory, hereditary, infectious, degenerative, and neoplastic categories. More than 25 precursor proteins have been identified whose structural variation can render them amyloidogenic and result in various diseases ranging from Alzheimer's dementia to familial amyloid polyneuropathy, prion disease, senile amyloid cardiomyopathy, and primary systemic amyloidosis. Several schemas have been used for clinical classification of these disorders. The conventional classification of amyloidosis divides the disease into systemic and localized forms. Systemic amyloidosis is further divided into primary, secondary, and familial (hereditary) types. This review focuses on the diagnosis and management of primary systemic amyloidosis.

Primary systemic amyloidosis is a fatal clonal plasma cell dyscrasia characterized by aberrant production of amyloidogenic immunoglobulin or its components. In

the most common form of primary systemic amyloidosis (>90% of cases), immunoglobulin light chain (AL) is the precursor protein; hence, the disorder is referred to as *AL amyloidosis*.²

ETIOLOGY AND EPIDEMIOLOGY

AL amyloidosis is a rare disease; each year nearly 3000 new cases are diagnosed in the United States, which translates into 9 cases per million persons.³ The exact etiology of AL amyloidosis remains unknown. The predominance of lambda light chain as the pathogenic light chain (kappa-to-lambda ratio of 1:3)⁴ and the use of a restricted repertoire of light chain variable region gene segments during the immunoglobulin gene recombination process by AL plasma cells are suggestive of a clonal selection process triggered by an as yet unidentified antigen.⁵ Interestingly, this restricted recombination is also hypothesized to impart relative organ tropism of the amyloidogenic light chain; for example, patients with clones from the 6a variable λ_{VI} germline gene segment are more likely to present with renal involvement.⁶ Most cases of AL amyloidosis present as de novo disease; a small fraction of cases evolve from preexisting multiple myeloma or, rarely, from other immunosecretory malignancies such as Waldenström's macroglobulinemia.⁷⁻¹⁰

CLINICAL FEATURES AND PRESENTATION

The clinical manifestations of AL amyloidosis result from organ dysfunction. The underlying basis for organ dysfunction is not completely understood, but pressure atrophy of the parenchymal tissue and direct cellular cytotoxicity are considered to be the major pathogenic mechanisms.¹² AL amyloidosis can affect virtually any organ, but most commonly it affects kidney, peripheral nerves, heart, gastrointestinal tract, liver, and soft tissues. Frequently, more than one organ is involved, and the number of involved organs has been associ-

ated with increased mortality.¹³ Since AL amyloidosis is a rare disease with presenting symptoms mimicking other common disorders, primary care physicians, and often specialists, do not include AL amyloidosis in the differential diagnosis. As a result, the diagnosis is frequently made in advanced stages, and this delay in diagnosis is the main reason for high mortality and morbidity associated with this disease.¹¹

The most common clinical syndromes associated with AL amyloidosis include nephrotic syndrome, congestive heart failure, and peripheral and autonomic neuropathy (Table 1). The presenting symptoms are often vague and include fatigue, dyspnea on exertion, edema, paresthesias, postural dizziness, and weight loss.^{14,15} The heart is the most common organ involved in AL amyloidosis, and patients frequently present with diastolic heart failure. Often, nephrotic-range proteinuria is the initial clinical feature discovered on urinalysis done as part of routine physical or insurance examination. Involvement of peripheral or autonomic nerves can result in disabling sensory neuropathy and orthostatic symptoms. Autonomic neuropathy or direct gastrointestinal tract involvement can cause formidable constipation or diarrhea associated with malabsorption. Amyloidosis should be suspected in every patient with chronic unexplained diarrhea and malabsorption, and clinicians should alert the pathologist of this suspicion so that colon or small bowel biopsies can be examined after proper staining with Congo red dye. Uncommon presentations include claudication of the jaw, calf, and limb, which occur due to small vessel involvement by amyloid deposits.¹⁰ Rarely, involvement of the small intramural blood vessels of the heart can produce exertional angina and myocardial ischemia.

Characteristic physical exam findings are very specific for AL amyloidosis but are present in a minority of patients. Macroglossia, a highly specific finding for AL amyloidosis was present in only 15% of patients in a large series.^{15,16} Salivary gland infiltration can occur and cause a sicca syndrome, which can be confused with Sjögren's syndrome.¹⁷ Amyloid purpura is classically located in the periorbital region, but can also be seen on the arms, legs, and neck. Hepatosplenomegaly is seen in a quarter of patients.¹⁸ Lower extremity edema can be indicative of nephrotic syndrome and/or heart failure. Patients can have the so-called *shoulder-pad sign*, which results from pseudohypertrophy of the muscles due to amyloid infiltration of the soft tissue.¹⁹ Similarly, periarticular amyloid deposition can result in thickening of synovium and periarticular soft tissue.²⁰ A small minority of patients can present with bleeding diathesis and coagulopathy, as extravascular amyloid

Table 1. Most Common Presenting Clinical Syndromes Associated with AL Amyloidosis

Recent-onset congestive heart failure, usually with normal ejection fraction
Albuminuria (with or without renal insufficiency)
Peripheral neuropathy (most commonly sensory but can be autonomic or motor)
Hepatomegaly with no identifiable etiology
Carpal tunnel syndrome (especially bilateral)
Macroglossia
Unexplained weight loss (occasionally associated with gastrointestinal symptoms of pseudo-obstruction or malabsorption)
"Atypical" multiple myeloma

can result in acquired deficiency of factor X. Patients with localized amyloidosis can present with symptoms attributable to infiltration of the area of involvement. For example amyloidomas in the laryngeal area result in hoarseness of voice, and infiltration of the lower urinary tract can result in hematuria.

Laboratory abnormalities commonly seen in AL amyloidosis include hypoalbuminemia (secondary to albuminuria) and elevated alkaline phosphatase (indicating liver involvement). With cardiac involvement, 2-dimensional echocardiography can reveal a thickened left ventricular wall (>12 mm), diastolic dysfunction, and occasionally a "granular sparkling" appearance of the myocardium.^{21,22}

DIAGNOSTIC EVALUATION

Presentation with any of the above mentioned syndromes warrants initiation of a workup for the diagnosis of AL amyloidosis. The initial step involves demonstrating the presence of monoclonal gammopathy. Serum protein electrophoresis (SPEP) is not an adequate screening test because monoclonal light chains are not identified on SPEP in approximately 50% of AL amyloidosis patients. When combined with urine protein electrophoresis (UPEP) with immunofixation, SPEP with immunofixation can identify 90% of patients with AL amyloidosis.²³ With the addition of the immunoglobulin free light chain assay, the detection rate in AL amyloidosis has improved to 96% to 99%.^{24,25}

If a monoclonal gammopathy and/or a skewed free light chain are identified, the next step in diagnosis is microscopic evaluation of appropriate tissue after staining with Congo red, as amyloidosis is a histologic

Table 2. Workup for AL Amyloidosis

Initial workup
Serum protein electrophoresis with immunofixation
Serum free light chain assay
24-hour urine collection (protein quantification and urine protein electrophoresis)
Complete blood count
Complete metabolic panel
Liver function tests
Skeletal survey
If above testing is suggestive of AL, proceed with the following:
Fat pad biopsy with Congo red stain
Bone marrow aspiration and biopsy with Congo red staining
Echocardiogram (magnetic resonance imaging of the heart in select cases)
Troponin-T
N-terminal pro-B-type natriuretic peptide (NT-proBNP)
Tests in select situations include: gastric emptying studies, autonomic reflex testing, nerve conduction studies, and selective organ directed biopsies

diagnosis. Since amyloid material is best demonstrated in the perivascular soft tissue and false-positive staining with Congo red can occur, it is imperative that an experienced pathologist examine adequate tissue with optimal staining technique. At Mayo Clinic, we are able to establish the histologic diagnosis in the majority of patients with subcutaneous fat pad aspirate and bone marrow biopsy.²⁶ The sensitivity of fat pad biopsy is 80% to 90%.²⁷ A bone marrow biopsy is done to rule out multiple myeloma, and can also identify amyloid deposits in 50% of patients if the specimen contains blood vessels.²⁸ In about 10% to 15% of cases, multiple myeloma can coexist with AL amyloidosis.²⁹ Biopsies from rectum, gingival mucosa, and minor salivary glands are also sometimes used to confirm the diagnosis. If the fat pad aspirate and bone marrow biopsy are negative, we typically proceed with biopsy of the involved organ.

Once the diagnosis of amyloidosis is confirmed, it is imperative to determine the molecular subtype (phenotype) of the amyloidosis to differentiate primary from familial and secondary amyloidosis, as the management and prognosis of these diseases differ. At Mayo Clinic, we determine the phenotype by laser micro-dissection and ionization/time-of-flight mass spectrometry that has a sensitivity and specificity of 98% to 100%.³⁰

After confirmation of AL amyloidosis, the next step is to determine the extent of organ involvement, as this

provides critical information about the prognosis and helps with treatment selection. Organ-specific workup is typically guided by the symptoms, and at a minimum includes 24-hour urine protein electrophoresis, electrocardiogram, and 2-dimensional echocardiogram and/or magnetic resonance cardiac imaging. In patients who have neuropathy and orthostatic symptoms, we include nerve conduction studies and autonomic reflex testing. All patients with AL amyloidosis should undergo coagulation screening as they can develop acquired factor X deficiency.

MANAGEMENT

Once the diagnosis of AL amyloidosis has been unequivocally established, the next step is to advise the patient about prognosis and devise and implement the treatment plan. It is important to note that patients presenting with localized amyloidosis who do not have evidence of systemic disease do not need systemic therapy and can be managed with local therapies such as surgery, radiation therapy, or endoscopic laser ablation.

PROGNOSIS

AL amyloidosis is a fatal disease with an historically dismal outcome of 20% survival at 5 years.^{3,31,32} Cardiac complications are the major cause of mortality (approximately 75%), and patients with symptomatic cardiac involvement have a 5-year survival of 2%. Adverse prognostic factors are listed in **Table 3**.^{31,33,34}

A major advancement in the management of AL amyloidosis patients has been the establishment of the uniformly accepted Mayo prognostic staging system.^{35–38} Using the biomarkers troponin-T (cutoff of 0.035 µg/L) and N-terminal pro-B-type natriuretic peptide (NT-proBNP; cutoff 332 pg/mL), this system stratifies patients into 3 stages: I (both markers low), II (1 marker high and 1 low), and III (both markers high).³⁹ Patients with stage I, II, and III disease had median survival of 26.4, 10.5, and 3.5 months, respectively. This system has retained its prognostic significance in patients undergoing high-dose therapy and stem cell transplant.⁴⁰ Recently, measurement of serum free light chain levels has become indispensable in determining the disease burden and treatment response in multiple myeloma. With the incorporation of free light chain measurement into the Mayo staging system of cardiac biomarkers, AL amyloidosis patients are stratified into 4 distinct stages, with prognosis ranging from 5.8 months for stage IV to 94.1 months for stage 0 disease (**Figure**).⁴¹

Table 3. Adverse Risk Factors Associated with AL Amyloidosis

Prognostic Factor	Comment
Clinical findings	
CHF and exertional syncope	Patients with exertional syncope and advanced CHF have a median survival of 3 to 4 months
Jaundice	Jaundice and hyperbilirubinemia are findings of advanced disease
Laboratory findings	
Howell-Jolly Bodies	Indicator of advanced disease
Circulating plasma cells	
Elevated beta-2 microglobulin	
Increased plasma cell labeling index	
dFLC >18 mg/dL	Important factors that have been incorporated into 4-stage prognostic model
Troponin-T >0.025 ng/mL	
NT-ProBNP >1800 pg/mL	
Echocardiogram findings	
Interventricular septum thickness	Median survival 1 year versus 4 years if thickness > or < 1.5 cm
Short mitral deceleration time	Poor outcome for patients with deceleration <150 ms
Decreased fractional shortening	Poor outcomes for patients with fractional shortening <20%

CHF = congestive heart failure; dFLC = difference between the involved and uninvolved serum free light chain; NT-ProBNP = N terminal of the pro-hormone of brain natriuretic peptide.

Recent studies have demonstrated that hematologic response, especially achievement of complete remission, is one of the strongest predictors of survival.^{33,42,43} The Mayo experience in patients who have undergone autologous stem cell transplant showed that a normalization of the affected free light chains after transplant was one of the best predictors of overall survival.⁴³ Similarly, Palladini and colleagues have noted improved survival with rapid hematologic response in AL patients not eligible for high-dose therapy.⁴⁴

Other established prognostic factors include beta-2 microglobulin,⁴⁵ circulating plasma cells,⁴⁶ plasma cell labeling index,⁴⁵ number of organ systems involved,^{13,47} and Howell-Jolly bodies on peripheral smear, a finding indicative of functional asplenia.⁴⁸

TREATMENT

Treatment of AL amyloidosis involves a multifaceted approach that includes organ-directed supportive care and anti-plasma cell therapy to stop production of the amyloidogenic protein. The success of systemic therapy in multiple myeloma has been translated into its effective use in AL amyloidosis; however, critical differences exist between these 2 distinct clinical entities. Evidence from the 1980s and early 1990s suggests that the transformed plasma cells in AL amyloidosis are much more sensitive to cytotoxic effects of chemotherapy than those of myeloma (*see* Chemotherapy section below). Furthermore, unlike myeloma, plasma cell prolifera-

tion in AL amyloidosis is minimal (average marrow involvement of approximately 7%),⁴⁹ and the primary problem is the production of “sticky amyloid proteins” that damage vital organs, making them much more susceptible to adverse effects of antimyeloma therapy. This difference also leads to the second major challenge in AL amyloidosis—how to assess response to treatment.

RESPONSE ASSESSMENT

Until recently, one of the greatest challenges in the management of AL amyloidosis had been the inability to uniformly assess response to treatment. The availability and standardization of serum measurements of cardiac biomarkers (NT-proBNP and troponin-T) and immunoglobulin free light chains have revolutionized the therapeutic paradigm by providing objective parameters that not only allow assessment of response to treatment, but also form the basis for disease staging and thereby allow objective comparisons of patients participating in clinical trials. Moreover, recent studies have identified these parameters as the most influential predictors of survival and risk associated with specific treatment.^{39,40}

A recent consensus panel devised a response assessment system that evaluates both the hematologic and organ response. Complete hematologic response is defined as no detectable monoclonal protein on SPEP and UPEP with immunofixation, normal free light chains, and bone marrow infiltration with less than 5% plasma cells. A partial response was defined as a

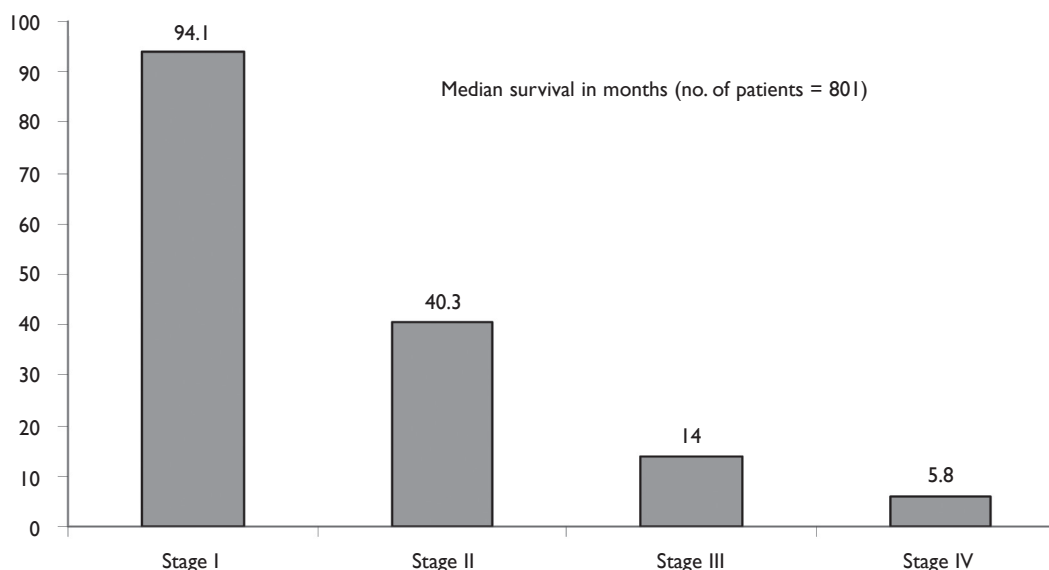


Figure. Revised prognostic score derived from 801 previously untreated patients with AL amyloidosis seen at the Mayo Clinic. Patients were assigned a score of 1 for each of dFLC (difference between involved and uninvolved free light chain) ≥ 18 mg/dL, troponin-T ≥ 0.025 ng/mL, and NT-ProBNP $\geq 1,800$ pg/mL, creating stages I to IV with scores of 0 to 3 points, respectively. The proportions of patients with stages I, II, III, and IV disease were 189 (25%), 206 (27%), 186 (25%), and 177 (23%). (Figure created from the data from Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol* 2012;30:989–95.)

50% reduction in either the serum M protein, urine M protein, and/or involved free light chains. A very good partial response (VGPR) was defined in the updated consensus opinion as a greater than 90% decrease in the difference between involved/uninvolved light chains (dFLC).⁵⁰ Palladini and colleagues⁵¹ investigated NT-proBNP as a surrogate marker of cardiac response and demonstrated that a 30% reduction and greater than 300 ng/L decrease from baseline correlated with improved overall survival. Additional indicators of organ response for cardiac involvement include a 2-mm decrease in the interventricular septal thickness and 20% improvement in the ejection fraction. Renal response is defined by a 50% decrease of the 24-hour urine protein. Liver response includes a 50% decrease in the alkaline phosphatase value and decrease in liver size by at least 2 cm.

SUPPORTIVE CARE

Organ dysfunction is the hallmark of AL amyloidosis, and organ-directed supportive care forms the cornerstone of disease management. Patients with congestive heart failure should be managed by judicious use of diuretics to relieve pulmonary and systemic venous con-

gestion. At times, the use of diuretics becomes challenging as autonomic neuropathy significantly precipitates diuretic-induced hypotension. Angiotensin-converting enzyme inhibitors are effective in modulating myocardial remodeling in congestive heart failure; however, they are often poorly tolerated by patients with AL amyloidosis who have advanced cardiac involvement. Use of inotropic agents should be carefully balanced against their arrhythmogenic potential; digitalis analogues have a special propensity to bind to amyloid fibrils, thereby significantly increasing their intracardiac concentration.⁵² Similarly, diltiazem should be avoided in cardiac amyloidosis as it can exacerbate heart failure.⁵³ Orthostatic hypotension can become a formidable problem in AL amyloidosis, and graduated compression stockings, fludrocortisone, and midodrine should be considered alone or in combination to maintain adequate venous return to avoid postural syncope.⁵⁴ Cardiac transplant has been used in select cases with varying success, but this is not a standard approach.^{55,56} Implantable cardiac defibrillators have also been used in the setting of depressed ejection fraction or malignant arrhythmias.⁵⁷

Diuretics are very useful for edema associated with nephrotic syndrome; however, patients should be care-

fully monitored for signs of low cardiac output resulting from low intravascular volume. In some resistant cases of nephrosis, renal artery embolization provides relief.⁵⁸ Use of dialysis for patients with renal failure due to AL amyloidosis results in inferior outcomes as compared to dialysis used for other causes of renal failure.⁵⁹ Renal transplantation has been performed in the setting of AL amyloidosis and should be considered in selected patients who have good systemic control of AL or in those patients who present with renal failure from isolated renal involvement by AL without additional organ involvement and can undergo stem cell transplant after kidney transplant.⁶⁰

Constipation and diarrhea are the most common symptoms related to AL amyloidosis of the gastrointestinal tract. Antidiarrheals (ie, loperamide, diphenoxylate, octreotide) have been used with varying success.⁶¹ Many patients with AL amyloidosis become malnourished because of gastrointestinal protein loss, which is associated with poor outcomes.

CHEMOTHERAPY

Systemic therapy directed against the transformed plasma cells has evolved over last 3 decades and has resulted in a modest improvement in 4-year survival of AL amyloidosis patients from 21% to 33%.⁶² While these advances are encouraging, 1-year mortality remains high, largely owing to delay in diagnosis and advanced cardiac involvement.

Alkylating agents and their combinations. Melphalan has been the prototype of alkylating agents used for the treatment of plasma cell dyscrasias, both in standard doses and as high-dose therapy with autologous stem cell rescue. In AL amyloidosis, several studies evaluating the combination of melphalan and steroids have demonstrated objective hematologic responses ranging from 18% to 64%,^{40,63–65} and more important this has been associated with improvement in organ function and survival. An important lesson learned from early studies is that unlike myeloma, the best steroid partner of melphalan for treatment of AL amyloidosis appears to be dexamethasone, as it is associated with higher response rates.⁴⁴ Hematologic responses are seen in up to two thirds of patients, with a complete response (CR) in one third. Updated data has demonstrated that melphalan and dexamethasone (MelDex) can result in significant long-term survival in AL amyloidosis patients, and thus remains the most widely used regimen for patients with AL amyloidosis who are not candidates for dose-intensive therapy.⁶⁵ The optimal duration MelDex therapy is 8 to 12 months, and it is generally well tolerated. The major complications include fatigue,

fluid retention from steroid use, hematologic toxicity, and the risk of secondary myeloid malignancies.

Cyclophosphamide is another alkylating agent commonly used for treatment of plasma cell dyscrasia. It is best used in combination with other antineoplastic agents, and unlike melphalan relatively spares hematopoietic precursors and stem cells. Cyclophosphamide is also combined at times with granulocyte-colony stimulating factor (G-CSF) for mobilizing hematopoietic stem cells in preparation for autologous peripheral stem cell transplant.

Recently, the bifunctional alkylating agent bendamustine has been shown to be effective in multiple myeloma. The preliminary data has indicated that it is also active in AL amyloidosis, but more mature data are needed to establish its role.⁶⁶

Proteasome inhibitors. The first-in-class proteasome bortezomib has been very effective in treating multiple myeloma and is approved for the treatment of newly diagnosed and relapsed myeloma patients. It has also demonstrated remarkable activity in AL amyloidosis. A phase II trial utilizing single-agent bortezomib demonstrated an overall response rate of 70% in relapsed/refractory AL patients.⁶⁷ The combination of bortezomib and dexamethasone has been evaluated in newly diagnosed and previously treated AL amyloidosis patients in 2 phase II trials.^{68,69} Hematologic response rates of 54% to 94% were noted, with 31% to 44% of patients achieving a CR. Addition of cyclophosphamide to a backbone of bortezomib and dexamethasone (CyBorD) has shown high response rates in multiple myeloma patients. Two relatively large retrospective series of AL amyloidosis patients treated with CyBorD revealed overall and complete hematologic response rates of 94% and 81% and 71% and 42%, respectively. Most important, the 2-year progression-free survival was 66% in previously untreated patients and few patients deemed unfit for stem cell transplant subsequently were able to get high-dose therapy.^{70,71}

There are 2 important limitations associated with the use of bortezomib in AL amyloidosis. First, long-term data about the durability of response, organ improvement, and survival are lacking. Second, AL amyloidosis patients are inherently at increased risk of cardiovascular, neurologic, and gastrointestinal toxicity due to bortezomib. Patients treated with bortezomib and steroid-containing regimens should be monitored for hypotension, worsening of congestive heart failure, and cardiac arrhythmias. In order to address these important issues, a phase III clinical trial comparing melphalan and dexamethasone alone versus in combination with bortezomib is ongoing in Europe.

Table 4. Challenges with the Use of Newer Agents in AL Amyloidosis

Novel Agent	Comments
Immunomodulatory agents (IMiDs)	All IMiDs have the potential to increase BNP (NT-proBNP) and response should be interpreted with caution
Thalidomide	Neurotoxicity and cardiotoxicity of thalidomide are significant
Lenalidomide	Rash and fatigue are prominent with lenalidomide
Pomalidomide	Lenalidomide and thalidomide doses used to treat myeloma are often not tolerated in AL amyloidosis
Proteasome inhibitor(s)	
Bortezomib	Bortezomib results in rapid reduction in light chains Can be given weekly or twice weekly and in patients with renal insufficiency
MLN 9708	Use should be carefully monitored in patients with advanced cardiac involvement Oral proteasome inhibitor under early phase investigation for patients with AL amyloidosis

Several next-generation proteasome inhibitors are at various stages of development for the treatment of hematologic malignancies. One such orally bioavailable agent, ixazomib (formerly MLN 9708), has undergone early investigations in relapsed AL amyloidosis patients, and encouraging initial results have paved the way for further evaluation as combination therapy.⁷² Carfilzomib, which is associated with significantly less neurotoxicity than bortezomib and was recently approved for the treatment of multiple myeloma patients with relapsed/progressive disease, is expected to have activity in AL amyloidosis patients.

Immunomodulatory (IMiDs) agents. IMiDs have made a profound impact in the management of several hematologic malignancies. Three IMiDs have been approved by the Food and Drug Administration for the treatment of various patient groups of multiple myeloma. These agents have also been evaluated in AL amyloidosis and have demonstrated consistent activity.

Thalidomide in combination with dexamethasone and as part of a triple-drug regimen with cyclophosphamide and dexamethasone has demonstrated activity in relapsed AL amyloidosis patients.^{73,74} Cardiotoxicity and neuropathy associated with use of thalidomide are particularly problematic in AL amyloidosis, and doses typically used to treat myeloma are not tolerated by AL amyloidosis patients. Due to a narrow therapeutic index and availability of effective alternatives, thalidomide is not commonly used for the treatment of AL amyloidosis in the United States.

Lenalidomide is more potent than thalidomide and is not associated with the significant cardiotoxicity or neurotoxicity typical of thalidomide. In a phase II trial,

lenalidomide in combination with dexamethasone was associated with a hematologic response rate of 67% in relapsed AL amyloidosis; one third of patients achieved a CR.⁷⁵ Similarly, the combination of lenalidomide, dexamethasone, and melphalan in a phase II trial showed a 42% hematologic CR in newly diagnosed AL amyloidosis.⁷⁶ In another phase II study, lenalidomide in combination with cyclophosphamide and dexamethasone demonstrated a 77% hematologic response rate with a median progression-free survival and overall survival of 28.3 and 37.8 months, respectively.⁷⁷ Like thalidomide, AL amyloidosis patients are not able to tolerate a full myeloma dose of lenalidomide due to significant fatigue and cutaneous toxicity.

Pomalidomide is the most recent agent in this group and is recently approved for the treatment of relapsed multiple myeloma patients. In a phase II trial, the combination of pomalidomide and dexamethasone resulted in a hematologic rate of 48% in patients with relapsed AL amyloidosis, where approximately half of patients had undergone prior stem cell transplantation. Fatigue and hematologic toxicity were the most commonly observed severe adverse effects.⁷⁸

Experience with novel agents is increasing in AL amyloidosis, but because each agent (or group of agents) is associated with unique challenges in this patient population it is imperative that well planned randomized studies are conducted to accurately establish their efficacy and, more importantly, safety profiles (**Table 4**).

STEM CELL TRANSPLANT

Exquisite sensitivity of plasma cells in AL amyloidosis to melphalan led to the hypothesis that dose-intensive treatment, as employed in multiple myeloma, may be

more effective than standard therapy. The feasibility of this approach was demonstrated by Comenzo et al⁷⁹ in a pilot study. Since then, several groups have reported on the safety and efficacy of this modality.^{80,81}

There is a dearth of data comparing high-dose therapy with standard chemotherapy, and only one prospectively conducted randomized trial has compared these strategies. In this multicenter European study, 100 patients with AL amyloidosis were randomly assigned to receive low-dose melphalan with dexamethasone versus high-dose melphalan followed by stem-cell rescue.⁴⁰ No significant difference in response rate or survival was noted, and transplant-related mortality was 24%. These data need to be interpreted carefully, as inclusion of patients with advanced cardiac involvement likely resulted in excessive transplant-related mortality. Recent data from 2 large centers has clearly demonstrated that patients who undergo high-dose therapy have good outcomes. In a large series of more than 450 patients who underwent high-dose chemotherapy, the 100-day transplant-related mortality (TRM) was 8.8% (compared to 1.4% for myeloma), with hematologic responses of approximately 80% and 40% CR. The 5-year survival rate was 66%. Achieving a CR or VGPR were statistical significant predictors of improved survival.⁸⁰ In another series, investigators from Boston University reported a 100-day TRM of 11.4%. Hematologic CR was noted in 34% of patients and was associated with the longest overall survival. Five-year survival was 86% for those who achieved a CR and 58% for those who did not achieve a CR.⁸¹ Depth of hematologic response, pre-treatment free light chain level, and the difference between involved and uninvolved free light chains remain the most important predictive/prognostic markers of post-transplant outcome.^{41,75,82,83}

While high-dose chemotherapy is associated with high response rate and prolonged survival, only a minority of patients qualify for this treatment as mortality and morbidity is significantly high compared to multiple myeloma. Unlike myeloma, 2 unique issues related to stem cell transplant in AL amyloidosis are fluid overload during stem cell mobilization with G-CSF and high incidence of gastrointestinal bleeding with the conditioning regimen. Investigators from Europe have reported treatment-related mortality as high as 40%.⁸⁴ However, as noted above, in experienced centers this mortality is significantly less; for example, at Mayo Clinic the treatment-related mortality is less than 10%. This is largely due to careful patient selection and the use of a risk-adapted approach.^{85,86} Typical contraindications for transplant include congestive heart failure, total bilirubin >3.0 mg/dL, ejection fraction less than

45%, or troponin-T >0.06 ng/mL. The relative contraindications include serum creatinine >2.0 mg/dL, interventricular septal thickness >15 mm, age >65 years, and more than 2 visceral organs involved with disease. Furthermore, additional transplant eligibility criteria include “physiologic” age ≤70 years, performance score ≤2, troponin-T <0.06 ng/mL, creatinine clearance ≥30 mL/min, New York Heart Association Class I or II, and no more than 2 visceral organs significantly involved.⁸⁵

CONCLUSION

AL amyloidosis remains a difficult disease to diagnose and treat. Delay in diagnosis remains the major hurdle in improving outcomes. AL amyloidosis should be kept in the differential diagnosis of any patient with nondiabetic nephrotic syndrome, restrictive-type cardiomyopathy, neuropathy, or unexplained hepatomegaly. Screening should be undertaken with SPEP and UPEP with immunofixation and measurement of free light chains. A positive screening should be followed with a bone marrow biopsy and fat pad aspirate with Congo red staining and confirmation of the immunoglobulin light chain origin by sensitive molecular diagnostic techniques. Prognosis is dependent on multiple factors, most importantly cardiac involvement (troponin-T and NT-proBNP) and number of organs involved at diagnosis. Organ-directed supportive care is very important. Anti-plasma cell treatment results in improvement in quality of life, organ improvement, and prolonged survival. Selected patients with AL amyloidosis who are candidates for high-dose chemotherapy and autologous stem cell rescue should be offered this modality, preferably at a center experienced in treating patients with AL amyloidosis. The use of novel agents is evolving in AL amyloidosis, and particular attention should be given to the unique toxicities of various agents specific to this disease.

BOARD REVIEW QUESTIONS

Test your knowledge of this topic. Go to www.turner-white.com and select Hematology from the drop-down menu of specialties.

REFERENCES

1. Kumar V, Abbas AK, Fausto N, Aster, JC, eds. Robbins & Cotran Pathologic Basis of Disease. 8th ed. Philadelphia: Saunders; 2010.

2. Gertz MA, Lacy MQ, Dispenzieri A. Amyloidosis: recognition, confirmation, prognosis, and therapy. *Mayo Clin Proc* 1999;74:490-4.
3. Kyle RA, Linos A, Beard CM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. *Blood* 1992;79:1817-22.
4. Merlini G, Stone MJ. Dangerous small B-cell clones. *Blood* 2006;108:2520-30.
5. Bellotti V, Mangione P, Merlini G. Review: immunoglobulin light chain amyloidosis—the archetype of structural and pathogenic variability. *J Struct Biol* 2000;130:280-9.
6. Comenzo RL, Zhang Y, Martinez C, et al. The tropism of organ involvement in primary systemic amyloidosis: contribution of Ig VL germ line gene use and clonal plasma cell burden. *Blood* 2001;98:714-20.
7. Rajkumar SV, Gertz MA, Kyle RA. Primary systemic amyloidosis with delayed progression to multiple myeloma. *Cancer* 1998;82:1501-5.
8. Dinner S, Witteles W, Witteles R, et al. The prognostic value of diagnosing concurrent multiple myeloma in immunoglobulin light chain amyloidosis. *Br J Haematol* 2013;161:367-72.
9. Pardanani A, Witzig TE, Schroeder G, et al. Circulating peripheral blood plasma cells as a prognostic indicator in patients with primary systemic amyloidosis. *Blood* 2003;101:827-30.
10. Gertz MA, Kyle RA, Noel P. Primary systemic amyloidosis: a rare complication of immunoglobulin M monoclonal gammopathies and Waldenstrom's macroglobulinemia. *J Clin Oncol* 1993;11: 914-20.
11. Kumar SK, Gertz MA, Lacy MQ, et al. Recent improvements in survival in primary systemic amyloidosis and the importance of an early mortality risk score. *Mayo Clin Proc* 2011;86:12-18.
12. Baden EM, Sikkink LA, Ramirez-Alvarado M. Light chain amyloidosis - current findings and future prospects. *Curr Protein Pept Sci* 2009;10:500-8.
13. Palladini G, Kyle RA, Larson DR, et al. Multicentre versus single centre approach to rare diseases: the model of systemic light chain amyloidosis. *Amyloid* 2005;12:120-6.
14. Kyle RA, Greipp PR. Amyloidosis (AL). Clinical and laboratory features in 229 cases. *Mayo Clin Proc* 1983;58: 665-83.
15. Kyle RA, Bayrd ED. Amyloidosis: review of 236 cases. *Medicine (Baltimore)* 1975;54:271-99.
16. Daoud MS, Lust JA, Kyle RA, Pittelkow MR. Monoclonal gammopathies and associated skin disorders. *J Am Acad Dermatol* 1999;40:507-35.
17. Jardinet D, Westhovens R, Peeters J. Sicca syndrome as an initial symptom of amyloidosis. *Clin Rheumatol* 1998;17:546-8.
18. Mohr A, Miehle S, Klauck S, et al. Hepatomegaly and cholestasis as primary clinical manifestations of an AL-kappa amyloidosis. *Eur J Gastroenterol Hepatol* 1999;11:921-5.
19. Liepnieks JJ, Burt C, Benson MD. Shoulder-pad sign of amyloidosis: structure of an Ig kappa III protein. *Scand J Immunol* 2001;54:404-8.
20. Alpay N, Artim-Esen B, Kamali S, et al. Amyloid arthropathy mimicking seronegative rheumatoid arthritis in multiple myeloma: case reports and review of the literature. *Amyloid* 2009;16:226-31.
21. Rahman JE, Helou EF, Gelzer-Bell R, et al. Noninvasive diagnosis of biopsy-proven cardiac amyloidosis. *J Am Coll Cardiol* 2004;43:410-5.
22. Siqueira-Filho AG, Cunha CL, Tajik AJ et al. M-mode and two-dimensional echocardiographic features in cardiac amyloidosis. *Circulation* 1981;63:188-96.
23. Gertz MA, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. *Am J Hematol* 2005;79:319-28.
24. Palladini G, Russo P, Bosoni T, et al. Identification of amyloidogenic light chains requires the combination of serum-free light chain assay with immunofixation of serum and urine. *Clin Chem* 2009;55:499-504.
25. Katzmann JA, Clark RJ, Abrahams RS, et al. Serum reference intervals and diagnostic ranges for free kappa and free lambda immunoglobulin light chains: Relative sensitivity for detection of monoclonal light chains. *Clin Chem* 2002;48:1437-44.
26. Gertz MA, Lacy MQ, Dispenzieri A, et al. Autologous stem cell transplant for immunoglobulin light chain amyloidosis: a status report. *Leuk Lymphoma* 2010;51:2181-7.
27. van Gameren II, Hazenberg BP, Bijzet J, van Rijswijk MH. Diagnostic accuracy of subcutaneous abdominal fat tissue aspiration for detecting systemic amyloidosis and its utility in clinical practice. *Arth Rheum* 2006;54:2015-21.
28. Stavem P, Larsen IF, Ly B, Rorvik TO. Amyloid deposits in bone-marrow aspirates in primary amyloidosis. *Acta Medica Scandinavica* 1980;208(1-2):111-3.
29. Kyle R. Multiple myeloma and other plasma cell disorders. In: Hoffman R, Benz EJ, Shattil SJ, et al, eds. *Hematology: basic principles and practice*. 2nd ed. Philadelphia: Churchill Livingstone.
30. Vrana JA, Gamez JD, Madden BJ, et al. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. *Blood* 2009;114:4957-9.
31. Gertz MA, Kyle RA, Greipp PR. Response rates and survival in primary systemic amyloidosis. *Blood* 1991;77:257-62.
32. Cohen AD, Comenzo RL. Systemic light-chain amyloidosis: advances in diagnosis, prognosis, and therapy. *Hematology Am Soc Hematol Educ Program* 2010;2010:287-94.
33. Lebovic D, Hoffman J, Levine BM, et al. Predictors of survival in patients with systemic light-chain amyloidosis and cardiac involvement initially ineligible for stem cell transplantation and treated with oral melphalan and dexamethasone. *Br J Haematol* 2008;143:369-73.
34. Kyle RA, Gertz MA. Primary systemic amyloidosis - clinical and laboratory features in 474 cases. *Sem Hematol* 1995;32:45-59.

35. Cueto-Garcia L, Reeder GS, Kyle RA, et al. Echocardiographic findings in systemic amyloidosis: spectrum of cardiac involvement and relation to survival. *J Am Coll Cardiol* 1985;6:737-43.
36. Kyle RA, Greipp PR, O'Fallon WM. Primary systemic amyloidosis: multivariate analysis for prognostic factors in 168 cases. *Blood* 1986;68:220-4.
37. Kyle RA, Gertz MA. Cardiac amyloidosis. *Int J Cardiol* 1990;28:139-41.
38. Dubrey SW, Cha K, Anderson J, et al. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. *QJM* 1998;91:141-57.
39. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol* 2004;22: 3751-7.
40. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med* 2007;357:1083-93.
41. Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol* 2012;30:989-95.
42. Lachmann HJ, Gallimore R, Gillmore JD, et al. Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy. *BJ Haematol* 2003;122:78-84.
43. Dispenzieri A, Lacy MQ, Katzmann JA, et al. Absolute values of immunoglobulin free light chains are prognostic in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. *Blood* 2006;107:3378-83.
44. Palladini G, Perfetti V, Obici L, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. *Blood* 2004;103:2936-8.
45. Gertz MA, Kyle RA, Greipp PR, et al. Beta 2-microglobulin predicts survival in primary systemic amyloidosis. *Am J Med* 1990;89:609-14.
46. Pardanani A, Witzig TE, Schroeder G, et al. Circulating peripheral blood plasma cells as a prognostic indicator in patients with primary systemic amyloidosis. *Blood* 2003;101:827-30.
47. Gertz MA, Zeldenrust SR. Treatment of immunoglobulin light chain amyloidosis. *Curr Hematol Malig Rep* 2009;4:91-8.
48. Gertz MA, Kyle RA, Greipp PR. Hyposplenism in primary systemic amyloidosis. *Ann Intern Med* 1983;98:475-7.
49. Perfetti V, Palladini G, Merlini G. Immune mechanisms of AL amyloidosis. *Drug Discovery Today* 2004;1:365-73.
50. Gertz MA, Merlini G. Definition of organ involvement and response to treatment in AL amyloidosis: an updated consensus opinion. *Amyloid-J Protein Folding Disorders* 2010;17:48-9.
51. Palladini G, Dispenzieri A, Gertz MA, et al. Validation of the criteria of response to treatment in AL amyloidosis. *Blood* 2010;116:586-7.
52. Rubinow A, Skinner M, Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. *Circulation* 1981;63:1285-8.
53. Gertz MA, Falk RH, Skinner M, et al. Worsening of congestive heart failure in amyloid heart disease treated by calcium channel-blocking agents. *Am J Cardiol* 1985;55 (13 Pt 1):1645.
54. Freitas J, Santos R, Azevedo E, et al. Clinical improvement in patients with orthostatic intolerance after treatment with bisoprolol and fludrocortisone. *Clin Auton Res* 2000;10:293-9.
55. Dey BR, Chung SS, Spitzer TR, et al. Cardiac transplantation followed by dose-intensive melphalan and autologous stem-cell transplantation for light chain amyloidosis and heart failure. *Transplantation* 2010;90:905-11.
56. Bradshaw SH, Veinot JP. Cardiac amyloidosis: what are the indications for transplant? *Curr Opin Cardiol* 2012;27: 143-7.
57. Kristen AV, Dengler TJ, Hegenbart U, et al. Prophylactic implantation of cardioverter-defibrillator in patients with severe cardiac amyloidosis and high risk for sudden cardiac death. *Heart Rhythm* 2008;5:235-40.
58. Solak Y, Polat I, Atalay H, Turk S. When urine is no longer beneficial: renal artery embolisation in severe nephrotic syndrome secondary to amyloidosis. *Amyloid* 2010;17: 24-26.
59. Moroni G, Banfi G, Montoli A, et al. Chronic dialysis in patients with systemic amyloidosis: the experience in northern Italy. *Clin Nephrol* 1992;38:81-5.
60. Kueenburg E, et al. Kidney transplantation in patients with chronic renal failure due to light chain deposition disease or AL amyloidosis. *Blood* 2001;98:309b-310b.
61. Poulos PD, Stollman N. Gastrointestinal amyloidosis: approach to treatment. *Curr Treat Options Gastroenterol* 2003;6:17-25.
62. Kumar S, Gertz MA, Lacy M, et al. Recent improvements in survival in light chain amyloidosis and the importance of an early mortality risk score. *Blood* 2010;19:116-121.
63. Kyle RA, Gertz MA, Greipp PR, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med* 1997;336:1202-7.
64. Skinner M, Anderson J, Simms R, et al. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med* 1996;100:290-8.
65. Palladini G, Russo P, Nuvolone M, et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. *Blood* 2007;110:787-8.
66. Palladini G, Schonland SO, Milani P, et al. Treatment of AL amyloidosis with bendamustine [abstract]. *Blood* 2012;120(21). Abstract 4057.
67. Reece DE, Hegenbart U, Sanchowala V, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a

- phase 1/2 study. *Blood* 2011;118:865–73.
68. Kastiritis E, Anagnostopoulos A, Roussou M, et al. Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone. *Haematologica* 2007;92:1351–8.
 69. Lamm W, Willenbacher W, Lang A, et al. Efficacy of the combination of bortezomib and dexamethasone in systemic AL amyloidosis. *Ann Hematol* 2011;90:201–6.
 70. Mikhael JR, Schuster SR, Jimenez-Zapada VH, et al. Cyclophosphamide-bortezomib-dexamethasone (Cy-BorD) produces rapid and complete hematologic response in patients with AL amyloidosis. *Blood* 2012;119:4391–4.
 71. Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression free survival. *Blood* 2012;119:4387–90.
 72. Merlini G, Sanchowala V, Zonder J, et al. MLN9708, a novel, investigational oral proteasome inhibitor, in patients with relapsed or refractory light-chain amyloidosis (AL): results of a phase 1 study. 2012. Available at <http://myeloma.org/pdfs/Merlini-731-3876.pdf>. Accessed July 23, 2013.
 73. Seldin DC, Choufani EB, Dember LM, et al. Tolerability and efficacy of thalidomide for the treatment of patients with light chain-associated (AL) amyloidosis. *Clinical Lymphoma* 2003;3:241–6.
 74. Wechalekar AD, Goodman HJ, Lachmann HJ, et al. Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood* 2007;109:457–64.
 75. Sanchowala V, Wright DG, Rosenzweig M, Finn KT. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. *Blood* 2007;109:492–6.
 76. Moreau P, Jaccard A, Benboubker L, et al. Lenalidomide in combination with melphalan and dexamethasone in patients with newly diagnosed AL amyloidosis: a multicenter phase 1/2 dose-escalation study. *Blood* 2010;116:4777–82.
 77. Kumar SK, Hayman SR, Buadi FK, et al. Lenalidomide, cyclophosphamide, and dexamethasone (CRd) for light-chain amyloidosis: long-term results from a phase 2 trial. *Blood* 2012;119:4860–7.
 78. Dispenzieri A, Buadi F, Laumann K, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. *Blood* 2012;119:5397–404.
 79. Comenzo R, Vosburgh E, Simms RW, et al. Dose-intensive melphalan with blood stem cell support for the treatment of AL amyloidosis: one-year follow-up in five patients. *Blood* 1996;88:2801–6.
 80. Dispenzieri A, et al. Patients with immunoglobulin light chain amyloidosis undergoing autologous stem cell transplantation have superior outcomes compared with patients with multiple myeloma: a retrospective review from a tertiary referral center. *Bone Marrow Transplant* 2013 April 22. [Epub ahead of print]
 81. Cibeira MT, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. *Blood* 2011;118:4346–52.
 82. Skinner M, Sanchowala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. *Ann Intern Med* 2004;140:85–93.
 83. Gertz MA, Lacy MQ, Dispenzieri A, et al. Effect of hematologic response on outcome of patients undergoing transplantation for primary amyloidosis: importance of achieving a complete response. *Haematologica* 2007;92:1415–8.
 84. Moreau P, Leblond V, Bourquelot P, et al. Prognostic factors for survival and response after high-dose therapy and autologous stem cell transplantation in systemic AL amyloidosis: a report on 21 patients. *Br J Haematol* 1998;101:766–9.
 85. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. *Blood* 2002;99:4276–82.
 86. Perfetti V, Siena S, Palladini G, et al. Long-term results of a risk-adapted approach to melphalan conditioning in autologous peripheral blood stem cell transplantation for primary (AL) amyloidosis. *Haematologica* 2006;91:1635–43.