MAYO CLINIC

Treatment of Immunoglobulin Light Chain Amyloidosis: Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Statement

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Abstract

Immunoglobulin light chain amyloidosis (AL amyloidosis) has an incidence of approximately 1 case per 100,000 person-years in Western countries. The rarity of the condition not only poses a challenge for making a prompt diagnosis but also makes evidenced decision making about treatment even more challenging. Physicians caring for patients with AL amyloidosis have been borrowing and customizing the therapies used for patients with multiple myeloma with varying degrees of success. One of the biggest failings in the science of the treatment of AL amyloidosis is the paucity of prospective trials, especially phase 3 trials. Herein, we present an extensive review of the literature with an aim of making recommendations in the context of the best evidence and expert opinion.

 ■ Mayo Clin Proc. 2015;90(8):1054-1081

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Immunoglobulin light chain amyloidosis (AL amyloidosis) and immunoglobulin heavy chain amyloidosis (AH amyloidosis) are typically low-tumor-burden plasma cell disorders characterized by deposition of insoluble fibrils composed of immunoglobulin chains. Most of the literature to date refers to AL amyloidosis because typing of amyloid fibrils on a case-by-case basis was uncommon until the 21st century. To date, there is no evidence for a clear difference in prognosis or presentation between AL and AH amyloidosis, so herein, both types will be referred to as AL amyloidosis.

Without treatment, AL amyloidosis has an inexorable progressive course due to uncontrolled organ damage. Although AL amyloidosis is the most common form of systemic amyloidosis, with an incidence of approximately 1 case per 100,000 person-years in Western countries,[1] there are other forms of systemic amyloidosis (Table 1).[2,3] Typing the amyloid is imperative because treatment strategies depend on the source of precursor protein.[4-6] In the case of systemic AL amyloidosis, the precursor protein is bone marrow plasma cell–derived immunoglobulin light (or rarely heavy) chains, and targeting plasma cells is the mainstay of therapy. In contrast, the next most commonly recognized forms of systemic amyloidosis are due to the precursor protein transthyretin, which is made in the liver. A disease phenotype similar to that of AL amyloidosis can be caused by either wild-type amyloid transthyretin (age related or wt-ATTR) or by mutated ATTR (hereditary or mut-ATTR).

Little is known about why amyloid targets specific tissues in one patient vs another.

Mayo Clin Proc. ■ August 2015;90(8):1054-1081 ■ http://dx.doi.org/10.1016/j.mayocp.2015.06.009
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TABLE 1. Classification of the Most Common Amyloidoses

Type of amyloidosis	Precursor protein component	Clinical presentation
AL (previously referred to as primary amyloidosis)[a]	κ or λ immunoglobulin light chain	Systemic or localized, see text
AH	γ, μ, α immunoglobulin heavy chain	Systemic or localized, see text
AA (previously referred to as secondary amyloidosis)	Serum amyloid A protein	Renal presentation most common; associated with chronic inflammatory conditions; typically acquired, but hereditary in cases of familial periodic fever syndromes
ALECT2	Leukocyte chemotactic factor 2	Renal presentation; acquired
ATTR		
Mutated transthyretin[b] (commonly referred to as familial amyloid polyneuropathy)	Mutant TTR	Hereditary; peripheral neuropathy, autonomic neuropathy, vitreous opacities, and cardiomyopathy
Wild-type TTR[b] (age-related or senile amyloidosis)	Normal TTR	Restrictive cardiomyopathy; carpal tunnel syndrome
Aβ2M	β_2-microglobulin	Carpal tunnel syndrome, arthropathy on large joints
Other hereditary amyloidoses		
AFib (also called familial renal amyloidosis)	Fibrinogen α-chain	Renal presentation
ALys	Lysozyme	Renal presentation most common
AApoA-I	A-I Apolipoprotein	Renal presentation most common
AGel	Gelsolin	Cranial neuropathy

[a]AL amyloidosis is the only form of amyloidosis that is secondary to a clonal plasma cell disorder; AL amyloidosis can be associated with multiple myeloma in approximately 10% to 50% of patients.
[b]TTR refers to transthyretin, which is commonly referred to as prealbumin.

Amyloid fibrils found in human tissues are not merely composed of pure amyloid precursor protein. Other proteins are found in the amyloid deposits, most commonly serum amyloid protein, apolipoprotein E, apolipoprotein A1, and apolipoprotein A4.[7]

The most important aspects of treating patients with AL amyloidosis are making a correct diagnosis as early as possible and finding the best chemotherapy and supportive trials for that individual patient. Clearly, clinical trials are the goal. In an environment with an absence of clinical trials, a paucity of randomized clinical trials, and an abundance of difficult and sometimes conflicting data, we present an extensive review of the literature with the aim of making recommendations in the context of the best evidence and expert opinion as we have done in the past for patients with multiple myeloma (MM)[8] and Waldenstrom macroglobulinemia.[9]

DIAGNOSIS OF AL AMYLOIDOSIS

The diagnostic biopsy sample may be from the tissue causing symptoms—eg, heart or kidney—or from a more accessible tissue, such as subcutaneous fat or bone marrow. The sensitivity of a biopsy sample from a symptomatic organ is higher than that from the more accessible tissues, ie, more than 95% for a symptomatic organ, 75% to 80% for fat, and 50% to 65% for bone marrow.[10] Special stains, such as Congo red, thioflavin T, and sulfated alcian blue, are required to recognize amyloidosis. The gold standard for amyloid diagnosis is Congo red avidity with apple-green birefringence under polarized light. Electron microscopy is also helpful

TABLE 2. Prognosis Is a Function of Organ Involvement and Plasma Cell Burden/Biology

End-organ damage	Plasma cell burden/biology
NT-proBNP, troponin[26-35]	Serum immunoglobulin FLC[18-22]
PS, NYHA class, exertional syncope[36,43,44]	Plasma cell burden[23]
Systolic blood pressure <100 mm Hg[36,45]	Cytogenetics[24,25]
Alkaline phosphatase, bilirubin, malabsorption[37-39]	
Creatinine, urine protein[40]	Deep hematologic response[46-50]

FLC = free light chain; NT-proBNP = N-terminal brain natriuretic peptide; NYHA = New York Heart Association; PS = performance status.

for identifying the 8- to 11-nm nonbranching fibrils.

Once a diagnosis of amyloidosis is made, the next equally important step is to type the amyloid, ie, determine the precursor protein by subjecting the amyloid to direct sequencing by mass spectrometry or immunostains such as immunogold, immunofluorescence, or immunohistochemical analysis. The presence of a serum or urine monoclonal protein does not ensure a diagnosis of AL amyloidosis and may lead to misdiagnosis in as many as 10% of cases.[11,12] Currently, we consider mass spectrometry the preferred method of typing the amyloid protein from tissues.[5,6]

Finally, the distinction between localized and systemic AL amyloidosis is required. The designation *localized* applies to those cases of AL amyloidosis in which the precursor protein (the immunoglobulin light chain) is made at the site of amyloid deposition (other than the bone marrow)[13-15] and is typically not associated with a detectable circulating monoclonal protein in the serum or urine. The mere absence of a monoclonal protein does not establish a diagnosis of localized amyloidosis. The classic examples of localized amyloidosis are tracheobronchial, urinary tract, cutaneous, lymph node, and nodular cutaneous involvement.[16] At Mayo Clinic, 8% of cases of amyloidosis were found to be localized.

EVALUATION OF PATIENTS WITH AL AMYLOIDOSIS

Tumor/Precursor Protein Burden

Screening for a monoclonal protein is done by serum immunoglobulin free light chain measurement and immunofixation studies of the serum and urine.[17] The distribution of immunoglobulin light chain variable gene use by bone marrow plasma cells is expected to be 2 to 1 κ to λ in the healthy population. Despite this, the number of AL amyloidosis cases favors λ to κ by 2 to 1, which supports the concept that germline λ is intrinsically more amyloidogenic than κ. A bone marrow aspirate to determine the extent of plasmacytosis along with fluorescent in situ hybridization (FISH) with a standard myeloma panel looking for trisomies, IgH translocations, and chromosome 1 duplications and deletions should also be performed. Baseline testing for measuring tumor burden should include serum and urine protein electrophoresis with immunofixation, serum immunoglobulin free light chain, and bone marrow aspirate and biopsy with FISH.[18-25]

Organ Involvement

The most commonly affected organs that experience symptoms are the heart, kidneys, skin, peripheral nerves, autonomic nerves, and liver. Minimum best practices to assess organ involvement would include a systems review and measurement of seated and standing blood pressure and levels of N-terminal brain natriuretic peptide (NT-proBNP), either troponin T or high-sensitivity troponin T, serum alkaline phosphatase, creatinine (or preferably estimated glomerular filtration rate), and 24-hour total urine protein.[26-40] Imaging with serum amyloid P is performed in limited countries in Europe and can provide an estimate of amyloid burden in the body but is not effective at estimating cardiac or peripheral (or autonomic) nervous system involvement. Tools used to assess the extent of cardiac involvement include NT-proBNP (and brain natriuretic peptide [BNP]), troponins, echocardiography with tissue strain, and magnetic resonance imaging.[16]

PROGNOSIS OF AL AMYLOIDOSIS

The prognosis of patients with AL amyloidosis depends on the burden of the amyloid in the tissues (especially the heart) and the size of the plasma cell clone and its biology, which predict the ability to achieve a hematologic and organ response (Table 2).[41,42] Cardiac involvement predicts most early deaths. Plasma cell biology predicts deaths occurring after the first year. During the past 40 years, the proportion of patients dying within 12 months of diagnosis remains fixed at approximately 30% to 40%, with

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TABLE 3. Mayo Risk Stratification Systems[a,b]

Stratification system	Troponin (ng/mL)	NT-proBNP (pg/mL)	Other	Parameters
Mayo 2004[26,27]	<0.035 Hs-Tnt <54 ng/L[34]	<332	…	Stage I = both low; stage II = either high; stage III = both high
European modification of Mayo 2004 stage III[36]	≥0.035	≥332 and ≤8500	Systolic BP >100 mm Hg	Stage IIIA = NT-proBNP ≤8500 pg/mL and BP >100 mm Hg Stage IIIB = neither A nor C Stage IIIC = NT-proBNP >8500 ng/mL and BP ≤100 mm Hg
Mayo 2012[55]	<0.025	<1800	dFLC 18 mg/dL	Stage I = all low; stage II = 1 elevated; stage III = 2 elevated; stage IV = all 3 elevated
Mayo 2013 transplant eligibility[56,57]	<0.06[c]	<5000[c]		For high troponin T, 100-d mortality is 25%-28% For high NT-proBNP, 10-mo mortality is 25%
Mayo 2015 transplant eligibility[d] (manuscript submitted)	<0.06[d]	Not included		Systolic BP <90 mm Hg is associated with 100-d TRM of 13% and 1-y TRM of 18%

[a]BP = blood pressure; dFLC = difference between involved and uninvolved serum immunoglobulin free light chain levels; Hs-Tnt = high sensitivity troponin T; NT-proBNP = N-terminal brain natriuretic peptide; TRM = treatment-related mortality.
[b]SI conversion factors: To convert troponin values to μg/L, multiply by 1.0; to convert NT-proBNP values to ng/L, multiply by 1.0.
[c]Exceptions may be made for patients with renal failure.
[d]Other eligibility criteria include physiologic age 70 years or younger; performance score of 2 or less; creatinine clearance of 30 mL/min/1.73 m^2 or greater (unless undergoing long-term dialysis); New York Heart Association class I/II; and more than 2 organs significantly involved.

the least improvement in overall survival (OS) noted over time for these sickest patients.[51] This early death rate largely explains why newly diagnosed patients tend to fare worse than patients with relapsed or refractory AL amyloidosis,[52] why patients seen at a referral center within 30 days of diagnosis have a median OS that is approximately half of that in those seen 30 days after diagnosis,[10] and why the risk factors for death are different during the first year and after the first year.[53]

PROGNOSTIC IMPACT OF CARDIAC INVOLVEMENT

The extent of cardiac involvement drives prognosis more than any other organ involvement, although symptomatic hepatic involvement and autonomic involvement also influence survival.[54] Soluble cardiac biomarkers have been accepted by the amyloid community as the best means by which to stage patients with AL amyloidosis; the most commonly used biomarkers include troponin T and NT-proBNP (Table 3).[26-35] Potential advantages of blood tests for assessing cardiac status include the reproducibility of the assays (in contrast to the interobserver variability of echocardiography), their ease of testing, and their relatively low cost. Aside from troponin T and NT-proBNP, there are data supporting the prognostic value of troponin I, BNP, and high-sensitivity troponin T.[26-33] There may be a role for using high-sensitivity troponin T alone in lieu of troponin T and NT-proBNP as a prognostic marker in the future.[34] Disadvantages of the cardiac biomarkers include the number of reagents available and potential limitations of the different assays, including a relative lack of sensitivity of troponin I, no current widespread clinical availability of high-sensitivity troponin T in the United States, a lack of standardization of the various BNP assays, and the inferior performance of NT-proBNP compared with BNP in the setting of renal dysfunction.[58-60] Palladini et al[61] offer useful solutions for dealing with cardiac biomarkers in renal failure by using higher cutoff values for NT-proBNP and BNP for detecting heart involvement and predicting survival. Aside from blood tests, clinical history is an important prognosticator. Patients with AL amyloidosis who present with florid congestive heart failure or syncope have median survival of 4 to 6 months.[43,44] Poor performance score, New York Heart Association (NYHA) class, and exertional syncope are all prognostic.[36,43,44]

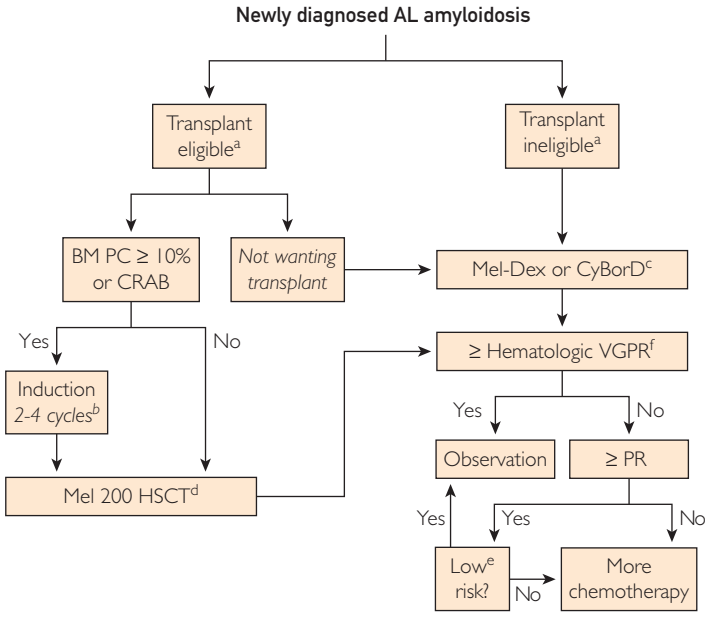

FIGURE 1. Nonstudy treatment algorithm for patients with newly diagnosed immunoglobulin light chain amyloidosis (AL amyloidosis). Note that many of the recommendations in this algorithm have not yet been supported by clinical trials; level of evidence is clearly indicated in the text. [a]To be transplant eligible, the following criteria should be met: physiologic age 70 years or younger; performance score of 2 or less; troponin T level less than 0.06 ng/mL, systolic blood pressure of at least 90 mm Hg; creatinine clearance of at least 30 mL/min (unless undergoing long-term dialysis), New York Heart Association class I/II, and no more than 2 major organs significantly involved (liver, heart, kidney, or autonomic nerve). [b]Induction also used if there is a delay in proceeding to autologous stem cell transplant or as clinically indicated. [c]If the hematologic parameter is not decreased by more than 50% at 2 months, consider changing therapy. [d]For age older than 70 years or creatinine clearance less than 30 mL/min/1.73 m^2, use melphalan 140 mg/m^2. [e]Mayo 2012 stage I or II. [f]Day 100 autologous stem cell transplant or after 4 to 6 cycles of chemotherapy. BM = bone marrow; CRAB = hypercalcemia, renal insufficiency, anemia, or bone disease; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; Dex = dexamethasone; dFLC = difference between involved and uninvolved serum immunoglobulin free light chain levels; HSCT = hematopoietic stem cell transplant; Mel = melphalan; PC = plasma cells; PR = partial response; VGPR = very good partial response.

Prognostic Impact of Serum Immunoglobulin Free Light Chains

Serum immunoglobulin free light chains are prognostic,[18-20] and they have been incorporated into the Mayo 2012 AL amyloidosis staging system (Table 3).[55] The Mayo 2012 staging system is used to identify patients with relatively low-risk (stages I and II) status in the treatment algorithm (Figure 1). Immunoglobulin free light chains are also a mainstay for evaluating hematologic response in AL amyloidosis.[42] The treatment of AL amyloidosis targets a reduction of involved free light chains to less than 4 mg/dL as a desired goal of therapy, and failure to achieve this level may prompt a change of therapy in some patients (Figure 1).

Prognostic Impact of Plasma Cell Burden and Biology

Recently, our group demonstrated that patients with greater than 10% bone marrow plasmacytosis regardless of CRAB (C = calcium elevated, R = renal dysfunction, A = anemia, or B = bone lesions) have inferior outcomes relative to patients with 10% or fewer bone marrow plasma cells and are now considered to have AL amyloidosis with MM.[62] The 10% cutoff point has been shown to markedly affect prognosis independent of serum immunoglobulin free light chain and cardiac biomarkers. Despite the patchiness of the bone marrow, using the estimation of bone marrow plasmacytosis seems to be a valuable prognostic marker and can be used to select patients who need induction therapy before stem cell transplant (SCT). Other plasma cell characteristics, such as proliferative rate and FISH, have also been shown to be prognostic, especially translocation t(11;14), which is associated with inferior survival.[63,64]

RATIONALE FOR THE RECOMMENDATIONS

Any recommendation for the treatment of AL amyloidosis is confounded by the disease's intrinsic heterogeneity, its rarity, and the paucity of randomized clinical trials. Despite these challenges, we believe that the combination of the literature and the experience of the authors, who are experts in the field, make these recommendations sound. Clinical trials should always be considered the first choice when available. In the absence of clinical trials, recommendations are as discussed herein (Appendix; Figure 1). Table 4 contains current hematologic and organ response criteria for patients with AL amyloidosis.[41,42]

Guideline. The goal of treatment (if cardiac involvement) should be a 30% reduction in NT-proBNP or better.

Level of Evidence. III

Mayo Clin Proc. ■ August 2015;90(8):1054-1081 ■ http://dx.doi.org/10.1016/j.mayocp.2015.06.009
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Grade of Recommendation. B

Guideline. The goal of treatment should be a hematologic response of very good partial response (VGPR) or better.

Level of Evidence. III

Grade of Recommendation. B

Prognostic Impact of Cardiac Response and Hematologic Response

Although cardiac responses can be documented by echocardiography, these responses are slow and relatively uncommon. Levels of NT-proBNP can drop rapidly, and a 30% reduction in NT-proBNP from a starting level of 650 pg/mL or higher is associated with a superior OS rate.[28,42]

In general, the deeper the hematologic response, the higher the likelihood of achieving an organ response and better OS. This has to be balanced by the morbidity and mortality of any given regimen considering the frail state of many of these patients.[42,65] Organ responses can occur with a hematologic partial response in as many as 30% to 56% of patients, and survival is markedly improved in patients achieving a partial response compared with no hematologic response. A major difficulty with organ response as a measure in many studies is that organ response is time dependent, ie, it can be much delayed.[65] Reports with less than 24 months of follow-up are likely to underreport organ response.

The most recent consensus is to aim for at least a VGPR (difference between involved and uninvolved serum immunoglobulin free light chain levels [dFLC], <4 mg/dL) or at least a 90% reduction in the dFLC if it can be achieved without excess therapy-related toxic effects.[46-50] At present, the mainstay of treatment is destruction of the underlying plasma cell clone, which, in turn, reduces or eliminates the amyloidogenic clonal immunoglobulin light chain. It had been assumed that the amyloid fibrils detected in tissue biopsy samples were the source of tissue injury and dysfunction and that chemotherapy produced improvement in organ function by shifting the equilibrium from fibril formation to fibril dissolution. That hypothesis has been challenged with the hypothesis that the clonal amyloidogenic light chains form toxic soluble intermediates responsible for the tissue damage.[66,67] In everyday clinical practice, this pathophysiologic debate is less relevant because there are currently no approved drugs that directly attack or dissolve the amyloid. The approach of using molecules or antibodies directed against serum amyloid protein or antibodies directed at the tertiary structure of the amyloid may be treatments of the future.[68-70]

The importance of a VGPR/complete response (CR) in AL amyloidosis exceeds the importance of a VGPR/CR in MM because response in both diseases is measured using circulating monoclonal immunoglobulin: for AL amyloidosis the circulating protein is the pathogen; for MM, it is merely a marker of clonal burden. The paradox, however, is that patients with AL amyloidosis are typically more frail than patients with MM, and

TABLE 4. Immunoglobulin Light Chain Amyloidosis Hematologic and Organ Response Criteria[42,a]

Response type	Criteria
Hematologic	
Complete response	Negative serum and urine immunofixation electrophoresis and Normal serum immunoglobulin κ/λ FLC ratio[b]
Very good partial response	dFLC <4 mg/dL[c]
Partial response	dFLC decrease ≥50%[d]
No response	Less than a partial response
Organ	
Cardiac response[e]	Decrease in NT-proBNP by >30% and 300 pg/mL (if baseline NT-proBNP >650 pg/mL) or a ≥2-point decrease in NYHA class (if baseline NYHA class III or IV)
Renal response	≥30% decrease in proteinuria or drop below 0.5 g/24 h in the absence of renal progression, defined as a >25% decrease in eGFR[f]
Hepatic response	50% decrease in abnormal alkaline phosphatase value or decrease in radiographic liver size by ≥2 cm

[a]dFLC = difference between involved and uninvolved serum immunoglobulin free light chain levels (a value adequate to measure response was deemed to be 50 mg/dL); eGFR = estimated glomerular filtration rate; FLC = free light chain; NT-proBNP, N-terminal brain natriuretic peptide; NYHA, New York Heart Association.

[b]Mandatory bone marrow removed from response criteria in 2012[42] compared with 2005[41] response criteria.

[c]New response criterion in 2012.[42]

[d]Serum M-spike relegated to secondary status and used only if no measurable involved serum FLC in 2012 criteria.

[e]Echocardiographic response replaced by NT-proBNP response in 2012.[42]

[f]New criteria proposed by the European amyloid community[40] suggesting replacement of the 50% reduction of proteinuria used in the 2005 criteria.

the pursuit of a VGPR/CR can be fraught with more morbidity and mortality.[71] Corticosteroids carry their own toxicities and can also worsen existing congestive heart failure or edema. Proteasome inhibition has not been prospectively studied in patients with advanced cardiac disease (NYHA class III or IV). Alkylators increase the risk of myelodysplastic syndrome.[72]

Whether long-term outcomes will differ depending on the means of arriving at a complete hematologic response is unknown.[73] This is most notable in the context of high-dose chemotherapy with autologous SCT (ASCT) vs standard-dose melphalan and dexamethasone (MDex). For patients achieving a hematologic CR, 5-year OS is approximately 70% regardless of the treatment modality used to achieve this depth of response.[46,74,75] For patients undergoing ASCT and achieving a CR, 10-year survival approaches 60%.[74] In a retrospective analysis studying patients who achieved a CR, there was a trend toward better OS in those treated with ASCT as their primary treatment,[65] but this finding is confounded by the fact that patients undergoing ASCT are highly selected and fit at baseline.

The final complexity to the VGPR/CR goal is that immunoglobulin light chains have varying degrees of amyloidogenicity and toxicity,[76-82] which are not measured in the clinic. The quest for a VGPR/CR may be less essential for patients with a less toxic or amyloidogenic protein, but currently this is not measurable.

INDICATIONS FOR THERAPY IN NEWLY DIAGNOSED AL AMYLOIDOSIS

Guideline. Treatment should be initiated immediately in virtually all patients with systemic AL amyloidosis.

Level of Evidence. III

Grade of Recommendation. A

No trials have been performed specifically to address this point, but it is known through randomized trials that patients with AL amyloidosis treated with chemotherapy live longer and can have clinical improvement compared with those who receive no therapy or ineffective therapy, such as colchicine.[83-86] Patients who have monoclonal gammopathy of undetermined significance or asymptomatic myeloma with an incidental finding of a positive Congo red of the bone marrow do not require immediate chemotherapy. Such patients can be observed every 3 months with an amyloid-directed review of systems, serum immunoglobulin free light chains, alkaline phosphatase, troponin, NT-proBNP, and creatinine as well as spot urine for albumin. At the first sign of organ involvement, therapy should be instituted.

INITIAL THERAPY FOR PATIENTS WITH SYSTEMIC AL AMYLOIDOSIS

Clinical trials should always be considered in the frontline setting if available. In the absence of clinical trials, recommendations are as discussed herein.

Autologous Stem Cell Transplant

Guideline. Consider high-dose chemotherapy with ASCT in selected patients.

Level of Evidence. III

Grade of Recommendation. B-C

In routine practice, the first question asked is whether a patient is a candidate for high-dose chemotherapy with autologous peripheral blood stem cell support (ASCT), not specifically because it is the best therapy but because it is the therapy that is most restrictive and that requires the most planning (Figure 1 and Table 3). Our opinion is that in young patients with low-risk disease, ASCT is an excellent option with the potential for long, event-free survival. There are, however, no randomized trial data to support that it is superior therapy; on the contrary, if the single small phase 3 French study addressing this question were accepted without critical analysis, one would conclude that ASCT is inferior to MDex.[73]

This trial was a prospective randomized study of 100 patients randomized to receive ASCT with high-dose melphalan conditioning compared with oral MDex.[73] Dose-modified melphalan was used based on the risk factors of the period[87] rather than on the more reliable cardiac biomarker methods. In this selected population, there was no difference between the 2 arms for hematologic response, and the landmark analysis performed to correct for the unexpectedly high early mortality associated with ASCT also showed no difference in OS.

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TABLE 5. Trials and Case Series of ASCT for Immunoglobulin Light Chain Amyloidosis[a,b]

Reference, year	Participants (No.)	Melphalan dose (mg/m^2)	TRM (%)	OHR/CR (%)	Median follow-up (mo)	Overall survival
Moreau et al,[91] 1998	21	140-200[c]	43	NR/14	14	4-y 57%
Goodman et al,[92] 2006	92	80-200[c]	23	37/20	NR	Median 5.3 y
Vesole et al,[89] 2006	107	>130[c]	27	32/16	NR	2-y 56%
Gertz et al, [93] 2004[d]	28	200	14	NR/NR	30	3-y 62%
Jaccard et al,[73] 2007[d]	50	140-200	24	52/24	36	2-y 48
Mollee et al,[45] 2004	20	140-200[c]	35	50/25	18	3-y 56%
Perz et al,[94] 2004[d]	24	100-200	13	54/46	31	3-y 83%
Perfetti et al,[95] 2006	22	100-200	14	55/36	73	5-y 56%
Cohen et al,[96] 2007[d]	42	100-200	4	60/20[e]	31	2-y 81%
Landau et al.[97] 2013[d]	40	100-200	10	55/27[e]	45	3-y 82%
Kim et al,[98] 2013	24	100-200	0	92/42[f]	NR	2-y 90%
Cibeira et al,[47] 2011	421	100-200	11	NR/34	48	Median 6.3 y
Dispenzieri et al,[99] 2013	454	100-200[c]	9	80/40	60	5-y 66%
D'Souza et al,[90] submitted	1536[g]	140-200	5-20	61/33	61	5-y 55%-77%

[a]ASCT = autologous stem cell transplant; CR = complete response; OHR = overall hematologic response; NR = not reported; TRM = treatment-related mortality.

[b]All the responses in this table are intention-to-treat.

[c]Alternative regimens, including melphalan/total body irradiation and busulfan, etoposide, cytarabine, melphalan, were used by some patients.

[d]Clinical trial.

[e]Response rates before consolidation. For the study by Cohen et al,[96] post-dexamethasone ± thalidomide OHR and CR rates increased to 60% and 21%, respectively; for the study by Landau et al,[97] after bortezomib and dexamethasone consolidation, OHR and CR rates increased to 79% and 58%.

[f]All but 1 patient received induction treatment.

[g]Registry data that may include patients from other series; the range of TRM and overall survival are period based, with the more recent period (2007-2012) having the lower TRM and higher overall survival and the oldest period (1995-2000) having the higher TRM and lower overall survival.

On an intention-to-treat (ITT) basis, median survival for MDex was 57 months and for ASCT was 22 months. This important study is limited by its small size for a disease that is as heterogeneous as AL amyloidosis. Of the 50 patients randomized to receive ASCT, only 37 actually received the planned transplant, and 9 of those died within 100 days, indicating unacceptably high (24%) treatment-related mortality (TRM), leaving only 28 patients for the landmark analysis. In contrast, of the 50 patients randomized to receive MDex, 43 received 3 or more cycles of therapy. Based on the small sample size and unexpectedly high TRM rate in this phase 3 trial, consideration must be given to the evidence obtained from patients reported from prospective single-arm studies, case-control series, observational studies, and registry studies numbering in the thousands (Table 5).[47,73,88-90]

The initial positive reports of ASCT came from Comenzo et al.[100] The concept of selection bias was initially raised[101] but then was settled with a case-control study[102] and favorable long-term outcomes.[47,99] The most commonly used conditioning regimen is melphalan 200 mg/m^2, although doses of 100 to 140 mg/m^2 have been used in sicker patients. With upfront ASCT without any induction therapy, hematologic responses have been reported anywhere from 32% to 68% and hematologic CRs from 16% to 50%.[47,49,73,88,89,100,103] Organ response is time dependent, and a median time to response can take up to 1 year, especially renal response, even in patients achieving a hematologic CR.[65] Organ response rates range from 31% to 64%. Patients with the deepest hematologic responses are more likely to have long-term survival.[46,47]

The Center for International Blood and Marrow Transplant Registry, which includes 1532 patients with AL amyloidosis treated with ASCT from multiple institutions—albeit within 24 months of diagnosis—found 100-day mortality that has reduced from 20% to 11% to 5% from the respective periods of

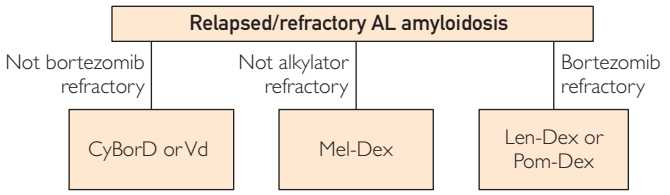

FIGURE 2. Nonstudy treatment algorithm for transplant-eligible patients with relapsed or refractory immunoglobulin light chain amyloidosis (AL amyloidosis). Note that many of the recommendations in this algorithm have not yet been supported by clinical trials; level of evidence is clearly indicated in the text. CyBorD = cyclophosphamide, bortezomib, and dexamethasone; Dex = dexamethasone; Len = lenalidomide; Mel = melphalan; POM = pomalidomide; Vd = velcade and dexamethasone.

1995-2000, 2001-2006, and 2007-2012.[104] The middle interval was a comparable period as the randomized French study, and those 595 Center for International Blood and Marrow Transplant Registry patients treated with ASCT had 5-year OS of 61% (95% CI, 57%-65%). Importantly, the survival rate continued to improve into the next interval of 2007-2012, with 5-year OS of 77% (95% CI, 72%-82%).

Guideline. Select candidates for ASCT based on troponin level, blood pressure, renal function, and physiologic age.

Level of Evidence. IV

Grade of Recommendation. B

As mentioned, the risk of TRM for patients receiving unattenuated high-dose melphalan approaches 50%. In our practice, we use a troponin T level greater than 0.06 ng/mL as an exclusion factor given 100-day all-cause mortality of 28% in such patients, in contrast to 7% all-cause mortality in those with a value below that threshold.[56,57] Another important contraindication for ASCT is low systolic blood pressure.[36,45] In our experience, systolic blood pressure of less than 90 mm Hg is associated with 3-month TRM of 14% (unpublished data; Dispenzieri et al); patients with systolic blood pressure of 100 mm Hg do not fare much better and should, therefore, be scrutinized carefully before recommending for ASCT. Patients with significantly impaired creatinine clearance are at risk for ASCT-associated renal failure.[105] Based on the existing ASCT data, the French randomized trial data, and data emerging from other therapies, we recommend excluding patients with high-risk features from ASCT (Figure 2 and Table 3). Collecting stem cells for storage can be considered in selected younger high-risk patients.

Guideline. Dose-attenuated conditioning chemotherapy with ASCT for sicker patients is not recommended outside of a clinical trial.

Level of Evidence. IV

Grade of Recommendation. B

In an effort to treat more patients with ASCT, dose-attenuated melphalan has been used in patients with AL amyloidosis with worse performance status, more organs involved, significant cardiac involvement, and older age. Consistently, this approach has resulted in lower hematologic response rates, including lower CR rates[47,106] despite reasonable TRM rates; the exception to this rule seems to be in patients who receive either induction or consolidation therapy (see later herein). The lower OS rates in patients taking attenuated-dose melphalan are not surprising because these patients were more frail before starting therapy, but the dose intensity of melphalan has also been shown to be important. In the Boston University cohort of 421 patients, patients receiving attenuated-dose melphalan had event-free survival of 21 months, which was less than half that of their full-dose melphalan counterparts.[47]

Our interpretation of the literature is that long-term event-free survival seems to be unsurpassed if ASCT is performed in select patients at high-volume transplant centers that are experienced enough with managing AL amyloidosis to have a low TRM rate,[47,88,93,95,102] especially if patients achieve a CR.[47,99] In contrast, for patients who have significant comorbidity related to their AL amyloidosis meriting consideration of reduction of conditioning melphalan dose intensity, based on data from the randomized controlled trial and single-arm outcomes from Mayo Clinic and Boston University, transplant is likely not a preferred initial option.[46,47,73,56,91,92]

Guideline. Induction therapy before ASCT for patients with less than 10% bone marrow

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plasmacytosis (AL amyloidosis without MM) is not universally recommended.

Level of Evidence. IV

Grade of Recommendation. B

Guideline. Induction therapy before ASCT for patients with 10% or greater bone marrow plasmacytosis (AL amyloidosis with MM) is recommended.

Level of Evidence. IV

Grade of Recommendation. B

To date, the use of induction chemotherapy before ASCT has been evaluated in only 4 prospective studies dealing specifically with this issue (Table 5). The trial that included bortezomib was considered positive, and the other 3 were negative.[107] We and others have shown that patients undergoing ASCT who achieve a CR without induction have exceedingly good outcomes, ie, 10-year OS of more than 70%.[99] In an analysis of the rates of CR and VGPR in patients with AL amyloidosis going directly to ASCT, we found that for patients with bone marrow plasma cell counts of 10 or less, the respective rates were 44% and 13%, whereas for patients with bone marrow plasma cell counts of 10 or greater, the respective rates were only 25% and 11%. In both groups, 6-year OS for patients with a CR was 88% to 89% (unpublished data; Dispenzieri et al). These data suggest that at least half of the patients with low tumor burden may not require additional therapy before ASCT (unpublished data; Dispenzieri et al).

Huang et al[107] reported on the use of 2 cycles of bortezomib and dexamethasone on days 1, 4, 8, and 11 every 21 days as induction vs no pretreatment before risk-adjusted melphalan and ASCT. The primary end point was achieved, with 65% of patients receiving bortezomib, dexamethasone, and ASCT and 36% of patients receiving ASCT only achieving a CR by 1 year. More important, however, the respective 2-year OS rates were 95% and 69%, and the respective 2-year progression-free survival rates were 81% and 51%. Two-year renal survival rates in the ASCT-only group were surprisingly low at 62%. However, on multivariate analysis, only troponin I—and not induction—was predictive of OS. There was only a trend toward benefit with bortezomib and dexamethasone induction, potentially due to small sample size.

Another test of bortezomib induction before ASCT had comparable CR rates. In this study, 35 patients were treated with biweekly bortezomib and dexamethasone for 2 cycles as part of a phase 2 study.[108] Five patients who were transplant eligible at enrollment had clinical deterioration during induction, necessitating withdrawal before ASCT. Those who underwent ASCT also had bortezomib included as part of their conditioning regimen. By ITT analysis, CR and VGPR rates were 55% and 16%, respectively.

In another prospective trial, which included 100 newly diagnosed patients considered candidates for ASCT, patients were randomized to receive either 2 cycles of oral melphalan and prednisone before ASCT or immediate ASCT.[109] With median follow-up of 45 months, the OS rate was no different between the 2 groups. Fewer patients received ASCT in the 2-cycle oral melphalan group because of disease progression during the oral chemotherapy phase of the study; this was particularly notable for patients with cardiac involvement. There was a trend toward an OS disadvantage with oral melphalan and prednisone in patients with cardiac involvement.

Similarly, a phase 2 trial by Perz et al[94] indicated that administering vincristine, doxorubicin, and dexamethasone for 2 to 6 cycles before high dose melphalan with SCT did not increase the hematologic response rate. Twenty-eight patients were included in the trial, but only 24 made it to stem cell chemomobilization and ASCT. Three-year OS from ASCT was 71% on an ITT basis. The authors concluded that this therapy seemed to be equivalent to that seen without previous induction therapy.

Guideline. Consolidation therapy for patients eligible for SCT can be considered in patients not achieving a VGPR or better.

Level of Evidence. IV

Grade of Recommendation. B

There are 2 tandem transplant trials and 2 chemotherapy trials addressing consolidative chemotherapy in AL amyloidosis after ASCT (Table 6). Sanchorawala et al[111] performed a prospective trial testing whether a second

TABLE 6. Induction and Consolidation Before and After ASCT[a]

Therapy	Participants (No.)	No previous Rx (%)	≥2 organs (%)	OHR/CR (%)[b]	Median follow-up (mo)	Overall survival
Induction						
B-Dex × 2 + ASCT[110]	28	100	59	86/68 vs	NR	2-y 95% vs
vs ASCT[110]	28			48/36		2-y 69%
Oral melphalan × 2 + ASCT[109]	48	100	74	NR/17	45	5-y 39%
vs ASCT	52			NR/21		5-y 51%
B-Dex × 2 + ASCT[108]	35	97	86	77[b]/57	36	5-y 84%
VAD[94]	28	89	54	43/39	31	3-y 71%
Consolidation						
Tandem ASCT[111]	53	85	>44	NR/60	43	4-y 80%[c]
Tandem ASCT[112]	68	87	62	6/NR	47-51	Median 68 mo/47 mo[d]
ASCT → thal-dex[96]	42	100-200	4	60/20[d]	31	2-y 81%
ASCT → bortezomib[97]	40	100-200	10	55/27[d]	45	3-y 82%

[a]ASCT = autologous stem cell transplant; B-Dex = bortezomib and dexamethasone; CR = complete response; NR = not reported; OHR = overall hematologic response; Rx = treatment; thal-dex = thalidomide-dexamethasone; VAD = vincristine, doxorubicin, and dexamethasone.

[b]Very good partial response or better.

[c]This value also includes the 9 patients who never received ASCT owing to inadequate stem cell collection; all other values are based on the 53 who received at least 1 ASCT.

[d]For patients with coexistent multiple myeloma.

consolidative (tandem) ASCT could induce a CR in patients who had not achieved a CR 6 months after a first ASCT with 200 mg/m^2 of melphalan. Sixty-two patients were enrolled: 9 did not receive a first ASCT owing to complications with collection or inadequate collection, 4 died within 100 days of a first ASCT, and 27 achieved a CR 6 months after the first ASCT. Seventeen patients had a second ASCT, with 1 dying within 100 days and 5 achieving a CR. The other 9 patients who had not achieved a CR with a first ASCT did not proceed to a second ASCT owing to patient choice or excessive nonhematologic toxicities during a first ASCT. The overall CR rate was 56% by ITT and 60% if one includes only the 53 patients who received at least 1 ASCT.

The second tandem trial and the 2 chemotherapy trials were designed to test the possibility of treating older or slightly sicker patients with attenuated-dose melphalan conditioning followed by either consolidative ASCT[112] or chemotherapy.[96,97] The tandem ASCT study using attenuated-dose melphalan (100 mg/m^2 per transplant) was a phase 2 trial that included 68 patients with AL amyloidosis. Fifty-nine patients were labeled as "AL amyloidosis only" because they had fewer than 30% bone marrow plasma cells and no CRAB, and 9 were called "AL amyloidosis with MM." The AL amyloidosis with MM group received induction with thalidomide and dexamethasone and was scheduled to receive maintenance with thalidomide and dexamethasone after a second ASCT, but it is unclear whether any patients made it to the maintenance phase. Just less than half of the AL amyloidosis—only group received a second ASCT, and 2 of 9 patients with AL amyloidosis with MM received a second ASCT. The OS was 68 months or 47 months for AL amyloidosis only or AL amyloidosis with MM, respectively, and median progression-free survival was 38 months and 16 months, respectively.[112]

The 2 phase 2 trials testing consolidative chemotherapy were from Memorial Sloan Kettering. In these trials, patients not achieving a CR received consolidative thalidomide ± dexamethasone[96] or bortezomib ± dexamethasone.[97] In the former study, 31 patients began consolidative therapy, with 52% completing 9 months of treatment and 42% achieving a deeper hematologic response. By ITT analysis, the overall hematologic response rate was 71% (36% CR), with 44% having organ responses.[96] In the latter study,

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17 of 23 patients undergoing ASCT received consolidative bortezomib and dexamethasone; overall, 74% achieved a CR and 58% had organ responses.[97]

The body of literature that demonstrates inferior survival in those not achieving the deepest responses would support the concept of consolidative therapy after ASCT in poor responders.[42] Whether the attainment of a deeper response is purely "prognostic"—demonstrating poor chemosensitivity and predicting shortened survival—or whether a deeper response can serve as a goal that will alter a patient's subsequent outcome has not yet been proved. The logic of the second supposition, however, is appealing from a pathogenic standpoint, ie, that the circulating free light chain is the source of organ damage through either direct toxicity or fibril formation; reducing the "toxin" should improve outcomes. Under the same premise, we recommend post-ASCT consolidation therapy in patients not achieving at least a VGPR at day 100 after ASCT or within 4 cycles of non-ASCT therapy.

Guideline. Maintenance therapy after ASCT is not recommended outside of clinical trials.

Level of Evidence. V

Grade of Recommendation. D

Because there are no trials or series addressing this question, we do not recommend post-ASCT maintenance therapy.

Guideline. Allogeneic hematopoietic SCT is not recommended outside of clinical trials.

Level of Evidence. V

Grade of Recommendation. D

Allogeneic hematopoietic SCT is not a standard therapy for patients with AL amyloidosis. There are no prospective clinical trials, only small case series.[113,114] The European Group for Blood and Marrow Transplantation registry reported 19 patients with AL amyloidosis who underwent allogeneic (n=15) or syngeneic (n=4) hematopoietic SCT between 1991 and 2003.[115] With median follow-up of 19 months, OS and progression-free survival rates were 60% and 53%, respectively, at 1 year. Forty percent of patients died of TRM.

Guideline for ASCT for Patients Undergoing Hemodialysis. An ASCT is feasible, especially if renal allograft is being considered.

Level of Evidence. V

Grade of Recommendation. B

Once a patient with AL amyloidosis has started dialysis, it is highly unlikely that renal function will ever return without a renal allograft. An ASCT can be performed safely in these patients as long as there is attention to dose adjustment of melphalan and supportive care medications. If there is even mild cardiac disease, the level of soluble cardiac biomarkers will be higher due to the impaired glomerular filtration rate, and the patient's cardiac status should be evaluated by other functional means to determine ASCT eligibility. All data supporting these recommendations are from case series[116] and personal experience, but TRM in selected patients ranges from 6% to 13%.[116] Comparable CR rates have been observed—53% in one series—but median OS in this same series was only 25 months. The 8 patients with a CR, however, had median OS of 4.5 years.

Guideline. An ASCT in patients with underlying lymphoproliferative disease or IgM monoclonal protein is a reasonable option.

Level of Evidence. V

Grade of Recommendation. B

Limited information exists to guide treatment. The largest transplant series is from Mayo Clinic; 22 of 434 patients with AL amyloidosis undergoing ASCT for AL amyloidosis had an IgM monoclonal protein in their serum.[117] Overall survival was comparable in IgM and non-IgM patients, although baseline characteristics between the 2 groups differed slightly. The IgM patients were older and were more likely to have peripheral neuropathy and lower involved free light chain and NT-proBNP levels. An ASCT is feasible, and either single-agent melphalan or busulfan, etoposide, cytarabine, melphalan conditioning can be considered in select patients.[118,119]

INITIAL THERAPY FOR PATIENTS INELIGIBLE FOR SCT

Clinical trials are again the preferred strategy; however, in the absence of a trial, a variety of options can be considered.

TABLE 7. Standard Chemotherapy for Immunoglobulin Light Chain Amyloidosis[a]

Therapy	Participants (No.)	No previous Rx (%)	≥2 organs (%)	OHR/CR (%)	Organ response (%)	Median follow-up (mo)	Median survival (mo)
MP[83-86,120]	~200[b]	Majority	NA	28	20-30	NA	18-29
VBMCP[120]	49	100	NR	29/NR	30	35	29
Melphalan IV[21]	20[c]			50	…		~50
Dex[121]	19	26	NR	53/31	16	27	11
Dex[122]	25	100	NR	40/12	12	18	13.8
Dex[123]	23	43	52	NR	35	33	24
Dex-IFN[124]	93	84	71	31/14	35	41	31
VAD[21,125-129]	32[c]	NR	NR	42-50	…	NR	…
Mel-Dex[48,75]	46	100	76	67/33	48	60	61
Mel-Dex[73]	50	100	68	72/24	39	36	60
Mel-Dex[130]	140[c]	100	NR	51/12	>20	60	20
Mel-Dex[29]	40[c]	100	80	58/13	NR	NR	10.5
Mel-IV-Dex[131]	61[c]	100	92	44/11	25	27	17.5
Mel-Dex[132]	70[c]	0	>50	26/8	NR	17	66% at 2 y

[a]CR = complete response; Dex = dexamethasone; IFN = interferon-alpha; IV = intravenous; Mel-Dex = melphalan and dexamethasone; MP = melphalan and prednisone; NA = not applicable; NR = not reported; OHR = overall hematologic response; VAD = vincristine, doxorubicin, and dexamethasone; VBMCP = vincristine, carmustine, melphalan, cyclophosphamide, prednisone.
[b]Conglomeration of multiple trials.
[c]Case series/reports.

Standard Chemotherapy

Regimen. MDex

Guideline. Valuable first-line option.

Level of Evidence. II

Grade of Recommendation. B

Regimen. Melphalan and prednisone

Guideline. Not recommended as first-line therapy because of the availability of better options.

Level of Evidence. IV

Grade of Recommendation. A-B

Table 7 demonstrates expected outcomes with standard chemotherapy.[48,73,75,83-86,120-132] Melphalan and prednisone doubled the OS rate compared with colchicine in 2 subsequent randomized trials, making it the standard therapy for most patients with AL amyloidosis until the mid-2000s.[85,86] Although only 18% of patients responded to melphalan and prednisone, organ responders enjoyed median survival of 89 months, whereas nonresponders had median survival of 15 months.[133] Multi-agent alkylator-based therapy (vincristine, carmustine, melphalan, cyclophosphamide, prednisone) did not improve OS rates,[120] but replacing prednisone with dexamethasone improved response and OS rates.[48]

In 2004, Palladini et al[48] reported their experience with MDex in patients who were not transplant candidates. Hematologic response rates of 67%, including 33% CRs, and organ response rates of 48% were reported.[48] These patients had median OS of 5.1 years and progression-free survival of 3.8 years.[75] The value of MDex was further validated in a prospective randomized study of 100 patients randomized to receive ASCT with high-dose melphalan compared with oral MDex.[73] In this highly selected population, on an ITT basis, median survival for MDex was 57 months.

Two other phase 2 studies examining MDex had markedly inferior results, with 3-month mortality of 23% and 28% and median OS of 10.5 and 17.5 months.[29,131] These 2 series included patients with severely impaired cardiac function as assessed by soluble cardiac biomarkers, demonstrating the relationship between patient selection and outcome.[101]

The historical concern for myelodysplastic syndrome in patients with AL amyloidosis receiving oral alkylators has been attenuated by

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more recent data demonstrating rates of myelodysplasia of 2.4%[48,75] rather than the historical rate of 7% of the total patient population, with 42-month actuarial risk of myelodysplasia or acute leukemia of 21%.[134] This lower rate is attributed to the modest total dose of melphalan administered (median, 288 mg; range, 48-912 mg), even considering the additional cycles delivered in relapsing patients.[48,75]

Immune Modulatory Drugs

Regimen. Thalidomide, cyclophosphamide, and dexamethasone

Guideline. Potential benefit as first-line therapy.

Level of Evidence. IV

Grade of Recommendation. B

Regimen. Thalidomide and dexamethasone

Guideline. Thalidomide and dexamethasone cannot be recommended as a first-line regimen.

Level of Evidence. V

Grade of Recommendation. B

Regimen. Thalidomide, melphalan, and dexamethasone

Guideline. Thalidomide, melphalan, and dexamethasone cannot be recommended as a first-line regimen.

Level of Evidence. II

Grade of Recommendation. B

Thalidomide as a single agent has heightened toxicity in patients with amyloidosis, and no hematologic or organ responses have been reported (Table 8).[135-137] In contrast, using thalidomide combined with dexamethasone, 48% of 31 patients achieved a hematologic response, with 8 organ responses (26%). Median time to response was 3.6 months (range, 2.5-8.0 months). Treatment-related toxic effects were frequent (65%), and symptomatic bradycardia was common (26%).[138] None of these patients were previously untreated.

In contrast, the UK group reported on prospective, observational studies of the combination of thalidomide with cyclophosphamide and dexamethasone.[139] A hematologic response occurred in 74% of 65 evaluable patients, including complete hematologic responses in 21%. With median follow-up of 22 months, median estimated OS from commencement of treatment was 41 months. Toxicity was not adequately assessed because this was not a clinical trial, and further study of this combination has shown it to be less well tolerated than previously thought.[140]

Palladini et al[141] treated 22 newly diagnosed patients with cardiac involvement with the combination of melphalan, thalidomide, and dexamethasone. Despite a hematologic response rate of 36%, only 20% of patients were alive at 1 year, and toxicity was significant.

Regimen. Lenalidomide and dexamethasone

Guideline. Not recommended as first-line therapy.

Level of Evidence. III

Grade of Recommendation. B

Regimen. Lenalidomide, melphalan, and dexamethasone

Guideline. Not recommended as first-line therapy except perhaps for patients with excellent performance status.

Level of Evidence. III

Grade of Recommendation. C

Regimen. Lenalidomide, cyclophosphamide, and dexamethasone

Guideline. Not recommended as first-line therapy.

Level of Evidence. III

Grade of Recommendation. C

Most of the lenalidomide data come from trials that combine previously untreated and previously treated patients with AL amyloidosis.[142-144] This makes interpretation of data in the newly diagnosed population impossible because, paradoxically, newly diagnosed patients with AL amyloidosis have inferior survival than

TABLE 8. Immunomodulatory Derivatives in Patients With Immunoglobulin Light Chain Amyloidosis[a]

Regimen	Participants (No.)	No previous Rx (%)	≥2 organs (%)	OHR/CR (%)	Organ response (%)	Median follow-up (mo)	Overall survival
Thal 200-800 mg[135]	16	6	31	25/0	0	NR	NR
Thal/Dex[138]	31	0	61	48/0	26	32	NR
Thal 200-800[137]	12	58	67	0	11	2[b]	NR
Thal 50-200[136]	18	28	50	0	11	6[b]	NR
Cycl/Thal/Dex[139]	65[c]	41	≥50	74/21	33	18	2-y 77%
Mel-Dex-Thal[141]	22	86	NR	36/5	18	28	1-y 20%
Len ± Dex[142]	22	43	57	43/5	26	17	2-y 50%
Len ± Dex[143]	69	6	52	47[c]/16	21	NR	NR[d]
Len ± Dex[144]	24	0	NR	38/0	4	23	1-y 50%
Len-Mel-Dex[148]	26	100	62	58/23	50	19	2-y 81%
Len-Mel-Dex[149]	25	92	≥50	58/8	8	17	1-y 58%
Len-Mel-Dex[150]	16	69	≥50	43/7	1	34	3-y 70% PFS 24 mo
Len-Cycl-Dex[151]	21	0	86	62/5	15	38	3-y 50% PFS 13 mo
Len-Cycl-Dex[152]	35	69	54	60/11	29	32	38 mo PFS 28 mo
Len-Cycl- Dex[153]	37	65	54	55/8	22	29	3-y ~33% 17 mo
Pom-Dex[154]	33	0	<2	48/3	15	28	28 mo PFS 14 mo

[a]CR = complete response; Cycl = cyclophosphamide; Dex = dexamethasone; IFN = interferon; Len = lenalidomide; Mel = melphalan; OHR = overall hematologic response; OS = overall survival; NR = not reported; PFS = progression-free survival; POM = pomalidomide; Rx = treatment; Thal = thalidomide.

[b]Median time receiving treatment.

[c]Partial response rate based on first 34 patients treated. No information on the additional 35 patients.

[d]Case series, not a clinical trial.

do patients with previously treated AL amyloidosis owing to the initial 30% to 40% death rate that occurs within the first 12 months of diagnosis.[16,51] With lenalidomide and dexamethasone, an overall hematologic response occurred in 38% to 47% of patients, with a CR in 5% to 16% and median OS ranging from 1 to 2 years. These and other trials have demonstrated that the starting dose of lenalidomide should be no higher than 15 mg/d administered on days 1 to 21 every 28 days. Because lenalidomide has been used to treat AL amyloidosis, serious cardiac and renal toxicity have been reported, making it imperative to consider drug toxicity rather than disease progression if patients taking lenalidomide deteriorate.[71,144-147] With the use of immunomodulatory drugs (IMiDs) in patients with AL amyloidosis, NT-proBNP and troponin levels frequently rise. Whether this rise is true cardiac toxicity or an epiphenomenon is unclear, but reversible clinical deterioration has been shown in patients treated with lenalidomide.[71]

The most promising of the lenalidomide, alkylator, dexamethasone combinations was that of melphalan, lenalidomide, and dexamethasone, which was used in 26 newly diagnosed patients with AL.[148] The population was highly selected because enrollment required an Eastern Cooperative Oncology Group performance status of 0 or 1. Fifty-eight percent of patients achieved a partial response, including 23% who achieved a CR. However, when Dinner et al[149] used this regimen in a less highly selected patient population, CR and OS were substantially lower. The Boston University group tested this same regimen in patients with newly diagnosed and previously treated AL amyloidosis and also found lower CR rates but fairly comparable OS rates.[150]

Results with cyclophosphamide, lenalidomide, and dexamethasone do not seem favorable, but selection criteria for these studies were less restrictive.[151-153] Applying these study results to the newly diagnosed population is also challenging because 2 of the studies included both newly diagnosed and previously treated patients,

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and the third included only previously treated patients. In these studies, hematologic response rates were approximately 60%, with CR rates of only 5% to 11%. Median OS for newly diagnosed and previously treated patients was 17 to 38 months.[151-153]

Regimen. Pomalidomide and dexamethasone

Guideline. Not recommended as first-line therapy.

Level of Evidence. V

Grade of Recommendation. D

The newest IMiD, pomalidomide, has been combined with dexamethasone and produced a hematologic response rate of 41%, including a 43% hematologic response rate in IMiD-refractory patients.[154] All the patients had received previous therapy, so the regimen has not been tested in the first-line setting. One-year OS and progression-free survival were 77% and 59%, respectively.

Proteasome Inhibitors

Regimen. Bortezomib ± dexamethasone

Guideline. This regimen can be used in newly diagnosed patients and in relapsed patients, but the safety of the regimen has not been systematically studied in patients with advanced cardiac disease.

Level of Evidence. IV

Grade of Recommendation. B

Regimen. Cyclophosphamide, bortezomib, and dexamethasone (CyBorD)

Guideline. This regimen can be used in newly diagnosed patients and in relapsed patients, but the regimen has not been systematically studied.

Level of Evidence. IV

Grade of Recommendation. B

Regimen. Bortezomib, melphalan, and dexamethasone

Guideline. This regimen can be used in newly diagnosed patients and in relapsed patients, but the regimen has not been systematically studied.

Level of Evidence. IV

Grade of Recommendation. C

Bortezomib seems to be a highly active treatment in patients with AL amyloidosis, but, to date, there are limited safety (or efficacy) data generated from prospective clinical trials. There is a paucity of high-quality data, but the enthusiasm for its use resulted in the publication of a variety of case series, included in Table 9.

The largest prospective clinical trial (CAN2007) evaluated single-agent bortezomib but included only a highly selected patient population.[156-158] Patients were excluded if they had no previous therapy, advanced cardiac disease (NYHA class III or IV), or baseline hypotension.[156-158] The CAN2007 trial evaluated 2 schedules of therapy, ie, the standard twice-weekly schedule (days 1, 4, 8, and 11 every 21 days) and a once-weekly schedule (days 1, 8, 15, and 22 every 35 days). The once-weekly schedule was preferred in terms of toxicity and dose delivered. Hematologic response rates were comparable at 67% and 68%, respectively. The CR rates favored the once-weekly schedule over the twice-weekly schedule 37% vs 24%. Median OS for the group was 63 months.

The only prospective randomized trial for patients with newly diagnosed AL amyloidosis that incorporates bortezomib ± dexamethasone required that patients be transplant eligible such that they could be randomized to receive either 2 cycles of bortezomib before proceeding to autologous stem cell transplant (ASCT) or immediate ASCT (see the discussion in the ASCT section).[110] In this highly selected population, the therapy was well tolerated.

The third prospective trial was a pilot for 10 patients with AL amyloidosis and an underlying lymphoproliferative disorder.[159] Most patients had previous therapy. The hematologic response rate was 78%, but there were no CRs, and 90% of patients were alive at 13 months.

The lion's share of the data comes from small retrospective studies and includes patients treated with either bortezomib alone or combined with dexamethasone as part of clinical practice. Once again, there is a mix of patients without clearly specified cardiac risk. The earliest summation of cases included 94 patients, mostly relapsed or refractory; the overall hematologic response rate was 72%, including a CR rate of 25% and an organ response rate of 30%.[161] A

TABLE 9. Proteasome Inhibitors in Patients With Immunoglobulin Light Chain Amyloidosis[a]

Regimen	Participants (No.)	No previous Rx (%)	≥2 organs (%)	OHR/CR (%)	Organ response (%)	Median follow-up (mo)	Overall survival
Bor-Dex × 2 + ASCT[110] vs ASCT[110]	56	100	59	86/68 vs 48/36	>65 vs >25	28	2-y 95% vs 2-y 69%
Bor-Mel-Dex vs Mel-Dex[155]	35 35	100	NR	76/NR 58/NR	NR	14	1-y 86%
Bor[156-158]	70	0	>44	63 (33)[b]	24[c]	52	4-y 67%
Bor-Ritux Dex[159]	10	60	40	78/0	0	13	1-y 90%
Bor-Mel-Dex[160]	17	100	NR	94/56	NR	11	NR
Bor ± dex[161]	94[d]	19	NR	72/25	30	12	1-y 76%
Bor + dex[162]	26[d]	69	65	54/31	12	15	Median 19 mo
Bor-Mel-Dex[163] vs Mel-Dex	87[d,e] 87[d,e]	100	≥50	69/42 51/19	NR	26	3-y 58% 3-y 45%
Bor-Cycl-Dex[164] vs Thal-Ctx-Dex	69[d,e] 69[d,e]	100	NR	71/40 80/25	NR	13 25	1-y 65% 1-y 67%
Bor-Cycl-Dex[165]	17[d]	58	82	94/71	NR	21	21-mo 71%
Bor-Cycl-Dex[166]	20[d]	100	NR	90/65	46	14	2-y 98%
Bor-Cycl-Dex[166]	23[d]	0		74/22			
Bor-Cycl-Dex[169]	60[d,f]	100	NR	68/17	32	12	1-y 57%
Bor-Cycl-Dex[167]	230[d]	100	NR	62/21	NR	NR	2-y 67%
Bor-Mel-Prednisone[168]	19[d]	100	90	84/37	47	8	2-y 39%

[a]ASCT = autologous stem cell transplant; Bor = bortezomib; Cycl = cyclophosphamide; Dex = dexamethasone; Mel = malphalan; NR = not reported; OHR = overall hematologic response; Rx = treatment.
[b]Excluding phase 1 patients.
[c]The denominator (n=62) for this calculation includes some of the 18 dose escalation patients because that group contained 5 of the 15 organ responses.
[d]Case series, not a clinical trial.
[e]Matched case-control studies.
[f]Retrospective look at patients with Mayo 2004 stage III disease.

subsequent retrospective study had a lower overall response rate but a comparable CR rate[162]; median survival, however, was more modest at 19 months[162] than 1-year OS of 76%.[161]

Bortezomib, Alkylator, and Corticosteroid Combinations

The fourth prospective clinical trial incorporating bortezomib included newly diagnosed and relapsed patients. It has been reported in abstract form only and is, therefore, very difficult to interpret.[160] The combination of melphalan, dexamethasone, and bortezomib has produced response rates of 94%, but follow-up is short and toxicity data are lacking.[160]

The remaing reports of combinations of an alkylator and bortezomib are all case series[165,166,168] and case-control series.[163,169] Case series of CyBorD have also been published with response rates of 93%,[165,166] but safety data are again sparse. In a recent retrospective case study from Europe that included 230 patients treated with CyBorD, the overall response rate was 60%, with 23% of patients achieving a CR on ITT analysis.[167] The most important risk factor for death was for patients with Mayo 2004 stage III who had an NT-proBNP level of 8500 pg/mL or higher (stage IIIb). Approximately 66% of these patients died by 12 months despite the fact that the hematologic response rate of the stage IIIb group was 42%, including 14% CRs. Thirty-nine percent of stage IIIb patients who had hematologic response still had cardiac progression. Patients with lower-stage disease did quite well, with none of the stage I patients dying in 3 years and more than half of the stage II and IIIa patients alive at 3 years.[167]

A case-control study comparing the outcome of 87 patients treated with bortezomib plus MDex (BMDex) with that of 87 controls treated with MDex was performed, matching on presence of cardiac and renal involvement, Mayo Clinic cardiac stage (2014), NT-proBNP level greater than or less than 8500 pg/mL, systolic blood pressure greater than or less than 100 mm Hg, treatment with full-dose dexamethasone (40 mg on days

Mayo Clin Proc. ■ August 2015;90(8):1054-1081 ■ http://dx.doi.org/10.1016/j.mayocp.2015.06.009
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1-4), estimated glomerular filtration rate greater than or less than 30 mL/min per 1.72 m^2, and dFLC greater than or less than 180 mg/L.[163] This study revealed a higher rate of CR with BMDex (42% vs 19%) but no survival advantage for the group as a whole (58% vs 45%; *P*=.4) or for the highest-risk patients.[163] With median follow-up of 26 months, separation of the survival curves did not occur in patient groups with NT-proBNP levels greater than 8500 pg/mL or NYHA class greater than II. The only group receiving bortezomib that fared significantly better than its case-matched cohort was the lowest-risk patients, but this observation is confounded by the fact that patients who received BMDex were from a later period—after 2009 (78% vs 32%)—a time when more treatment options were available and possibly lead time bias related to earlier recognition in a later cohort; in toto, only 18 of the patients treated with MDex received bortezomib as second-line therapy. The authors concluded that intermediate-risk patients who are not fit enough to receive high-dose dexamethasone are likely to obtain the greatest advantage from the addition of bortezomib to MDex.

The other matched case-control study was performed by Venner et al.[164] They compared 69 patients treated with CyBorD with 69 patients treated with cyclophosphamide, thalidomide, and dexamethasone (CTD) in the frontline setting.[164] Patients were matched based on Mayo cardiac stage (2004), and they aimed to have similar proportions of patients with high dFLC and ultra-high NT-proBNP levels, ie, 8500 pg/mL. Their routine practice was to change regimens if a 90% reduction in dFLC was not achieved after 3 cycles of therapy. A higher percentage of patients treated with CTD were switched to an alternative therapy based on these groups (20% vs 1%). All but 1 patient treated with CTD received a bortezomib-containing regimen as second-line therapy. On an ITT basis, overall response rates were 71% vs 80% in the CyBorD vs CTD arms (*P*=.32). A higher CR rate was observed in the CyBorD arm vs the CTD arm (40.5% vs 24.6%; *P*=.046). Approximately 25% of patients died within 3 months of starting therapy. One-year OS was 65% for CyBorD and 67% for CTD (*P*=.87), with median follow-up of 13 and 25 months, respectively. There was no difference in OS by treatment even when patients were considered by whether they had very high NT-proBNP levels. Median progression-free survival was 28.0 months for CyBorD and 14.0 months for CTD (*P*=.04).

In a recent analysis of patients with newly diagnosed Mayo 2004 stage III,[169] 1- and 2-year OS rates were estimated for patients treated with different regimens. These authors note the following anticipated 1- and 2-year OS rates, respectively, with various regimens in patients with stage II or II/III: cyclophosphamide + lenalidomide + dexamethasone, approximately 40% and 20% to 24%; CTD/MDex, 46% and 29%; melphalan + lenalidomide + dexamethasone, 22% and 22%; and CyBorD, 57% and 51%. Caveats to this analysis are that most of these data were gleaned from small numbers of patients in observational studies treated over a long period rather than from prospective clinical trials, making selection and reporting bias important confounders.

Other proteasome inhibitors—eg, carfilzomib or ixazomib—may also provide benefit for patients with AL amyloidosis, but there are inadequate data to make any recommendations in the upfront setting at this time.

NON-ASCT THERAPY FOR PATIENTS WITH AL AMYLOIDOSIS WITH UNDERLYING LYMPHOPROLIFERATIVE DISEASE OR IgM MONOCLONAL GAMMOPATHY

Regimen. Rituxan, bortezomib, and dexamethasone.

Guideline. Potential benefit as first line therapy.

Level of Evidence. V

Grade of Recommendation. B

Regimen. CyBorD as first line

Guideline. Potential benefit as first line therapy.

Level of Evidence. V

Grade of Recommendation. B

IgM-associated AL amyloidosis is a rare clinical entity with distinctive clinical characteristics. Many cases may be localized forms, in which there is only nodal or soft-tissue involvement

without visceral involvement. Many of these cases can merely be observed, but observed more aggressively if there is a circulating monoclonal protein and especially if there are circulating monotypic serum immunoglobulin free light chains. Chemotherapy is more often reserved for cases in which there is typical amyloid deposition in viscera or the nervous system. Historically, regimens have been borrowed from the myeloma and Waldenstrom macroglobulinemia armamentaria, but they have not been tested systematically given the rarity of IgM-associated AL amyloidosis. These treatments have included single agents and combinations of cladribine, fludarabine, rituximab, chorambucil, cyclophosphamide, vincristine, doxorubicin, oral melphalan, corticosteroids, and ASCT.[118,170,171]

In a retrospective series of 77 patients there was a 32% response rate, with no CRs, and it seemed that the oral alkylators had the lowest response rates.[171] Overall survival was 49 months. In another series of 15 patients, 3-year OS was 58%.[118] Until the incorporation of bortezomib, complete hematologic responses had been rare, but patients have achieved organ response rates and OS rates comparable with patients with pure plasma cell disorders.

There are 2 reports of incorporating bortezomib into the treatment of these patients. The first is a pilot study from Palladini et al.[159] They treated 10 patients with IgM AL amyloidosis with rituximab, bortezomib, and dexamethasone.[159] Hematologic response was achieved in 78% of patients, including 3 refractory to previous rituximab therapy. Two patients had normalization of their κ to λ ratio, but none achieved negative immunofixation. With median follow-up of 13 months, 1 patient died.

The second report including bortezomib was that of 8 Japanese patients treated with CyBorD.[172] Four patients had a CR, 2 had a VGPR, and 2 had a partial response. Five of 6 patients (83%) had organ responses in the heart or kidney.

Bendamustine and ibrutinib may also be candidates for study in this patient population.

TREATING RELAPSED OR REFRACTORY AL AMYLOIDOSIS

Guideline. Base salvage therapies on previous therapies, with the aim of introducing drugs with other mechanisms of action to treat relapsed or refractory AL amyloidosis.

Level of Evidence. V

Grade of Recommendation. C

Overall, patients receiving second-line therapy do better than patients receiving first-line therapy owing to the very high death rate that occurs within the first 6 months of diagnosis. Clearly, getting a rapid and deep hematologic response is better than not, but patients who are physically more resilient survive to receive second- or higher-line therapy. The treatments outlined in Tables 5, 7, 8, and 9 contain a mix of newly diagnosed and previously treated patients. Patients not refractory to bortezomib should receive a bortezomib-containing regimen (Figure 2). Those who are not alkylator refractory are candidates for MDex. For patients who are bortezomib refractory, lenalidomide and dexamethasone or pomalidomide and dexamethasone are recommended.

SUPPORTIVE THERAPY FOR AL AMYLOIDOSIS

Guideline. Diuretics are the mainstay of supportive care for cardiac AL amyloidosis.

Level of Evidence. IV-V

Grade of Recommendation. D

Guideline. β-Blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and calcium channel blockers should be used with great caution (or not at all) in cardiac AL amyloidosis.

Level of Evidence. V

Grade of Recommendation. D

There are special considerations in patients with cardiac amyloidosis. These patients typically have severe diastolic dysfunction, with a nondilated ventricle leading to increased filling pressures, often with low cardiac output. The use of standard medical therapy for heart failure with reduced ejection fraction, specifically, β-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, often worsen patients' clinical status. Diuretics are the mainstay

Mayo Clin Proc. ■ August 2015;90(8):1054-1081 ■ http://dx.doi.org/10.1016/j.mayocp.2015.06.009
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of care, with the best results achieved with a combination of loop diuretics and spironolactone. Metolazone or periodic thoracentesis may be considered in select cases.[173] β-Blockade may cause profound hypotension and low cardiac output and should be avoided. Afterload reduction with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers also tends to be poorly tolerated in patients with cardiac AL amyloidosis, especially in those who have orthostatic hypotension due to autonomic neuropathy.

Patients with cardiac amyloid are at risk for intracardiac thrombi[174,175]; in one study, 35% of patients with AL amyloidosis who had transesophageal echocardiograms had atrial thrombi, most of which were located in the right or left atrial appendages.[175] Anticoagulation should be considered, recognizing that life-threatening bleeding is a potential risk.

For patients with atrial fibrillation, rate control can be a challenge because β-blockade and calcium channel blockers are often poorly tolerated. Digoxin has been considered contraindicated in cardiac amyloidosis due to concerns regarding digoxin binding and an increased risk of toxic effects,[176] but digoxin is often preferred over calcium channel blockers and β-blockers for rate control in atrial fibrillation. Nondihydropyridine calcium channel blockers should be avoided due to their associated bradycardia and negative inotropic effects.[177] In our experience, amiodarone is often helpful for rhythm control, and selected patients may benefit from atrioventricular node ablation with permanent pacing. Patients with cardiac amyloidosis are susceptible to malignant arrhythmias, including ventricular tachycardia, ventricular fibrillation, and pulseless electrical activity.[178,179] The role of implantable cardioverter defibrillators is controversial in these patients because both successes and failures have been documented.[179-182] Although appropriate implantable cardioverter defibrillator device therapy has been observed in patients with AL cardiac amyloid, studies to date have not demonstrated a survival advantage.[183] A study of implanted cardiac rhythm recorders found that sudden death in AL amyloidosis is commonly due to pulseless electrical activity, often preceded by bradycardia.[184] Given the absence of randomized studies, the role of implantable cardioverter defibrillator therapy for primary prevention in cardiac AL amyloidosis remains unclear.

Guideline. Diuretics are the mainstay of supportive care for renal AL amyloidosis.

Level of Evidence. V

Grade of Recommendation. D

In patients with renal involvement, which is nephrotic syndrome in most, the major problem is third space fluid distribution due to hypoalbuminemia. This may be further exacerbated by coexisting cardiomyopathy. Diuretics are the mainstay of therapy. It is not unusual for nephrologists to institute an angiotensin-converting enzyme inhibitor based on their management of diabetic nephropathy. There are no data to support this intervention in AL amyloidosis. Adequate suppression of the underlying clone is the most important maneuver to improve renal function.[185] Patients undergoing dialysis may struggle with hypotension, which can be successfully managed with predialysis midodrine.

Guideline. A trial of drugs used to treat symptoms of small fiber neuropathy many be warranted in patients with peripheral nerve involvement.

Level of Evidence. V

Grade of Recommendation. D

Guideline. Midodrine and pyridostigmine can help with orthostasis related to autonomic dysfunction.

Level of Evidence. II

Grade of Recommendation. B

Patients with amyloidosis with neuropathy typically have small fiber involvement, which can be treated symptomatically with amitriptyline, nortriptyline, gabapentin, pregabalin, or duloxetine. Topical preparations that include various combinations of lidocaine, ketamine, and amitriptyline may also provide relief. For patients with neuropathy due to carpal tunnel syndrome, carpal tunnel release or carpal tunnel braces are of benefit. The autonomic insufficiency can be difficult to manage, especially in patients with severe

nephrotic syndrome or severe cardiomyopathy. Fludrocortisone and salt tablets are useful only in a few of these patients because they may aggravate congestive heart failure or peripheral edema. The α-1 receptor agonist midodrine or the anticholinergic pyridostigmine can improve neurogenic orthostatic hypotension,[186] and metoclopramide, used in diabetic gastroparesis, can help with gastric emptying.

Guideline. Consider doxycycline the prophylactic antibiotic of choice.

Level of Evidence. IV

Grade of Recommendation. B

Two retrospective studies were performed studying outcomes of patients with AL amyloidosis who were treated with doxycycline.[187,188] The justification for the hypothesis that doxycycline might provide benefit in patients with AL amyloidosis was derived from in vitro ATTR studies[189] and ATTR[189] and AL amyloidosis[190] mouse model studies.[190,191] In vitro doxycycline causes TTR fibril disruption. The first report was that of Kumar et al,[192] who reviewed outcomes of patients undergoing ASCT for AL amyloidosis. Doxycycline was used as prophylaxis in 106 of the patients with AL amyloidosis (23%) undergoing ASCT between 1996 and 2011, with most of the remaining patients receiving penicillin. The usual reason for using doxycycline was a history of penicillin allergy. Median OS for the entire cohort was 161 months (95% CI, 101-not reported). Median OS for those receiving doxycycline prophylaxis was not reached compared with 113 months for the remaining patients (P=.09). Looking specifically at patients with a hematologic response, median OS was not reached for the doxycycline group compared with 161 months for the remaining patients (P=.04). Similarly, Wechalekar et al[193] performed a case-matched study of newly diagnosed patients with AL amyloidosis with advanced cardiac involvement who received doxycycline prophylaxis in addition to frontline chemotherapy with those who did not. They identified 16 patients and 22 controls, all of whom were treated with bortezomib-based therapy. Twelve-month OS was 94% in the doxycycline-treated group but only 55% in the group without doxycycline.

ORGAN TRANSPLANT

Solid organ transplant is a controversial intervention in patients with AL amyloidosis. Because the disease is systemic and presumably incurable, there is concern that the amyloid will either reoccur in the transplanted organ or progress in another organ, resulting in a poor outcome. The best outcomes have occurred in the setting of careful patient selection, excluding patients with clinically evident multiorgan involvement, and in those who received chemotherapy to eradicate the clone either before or after the solid organ transplant.

Guideline. Cardiac transplant for AL amyloidosis can be considered in very select patients.

Level of Evidence. V

Grade of Recommendation. C

The results of orthotopic cardiac transplant are mixed.[16] Recommendations are derived from fewer than 100 transplants described in 8 series. Five-year OS ranges from 18% to 65%. Key determinants for the best outcomes include limiting candidates to those who have lower tumor burden and clinical organ involvement limited to the heart and administering chemotherapy that is effective against the clone. Most patients do not satisfy these criteria, and even those who are placed on a transplant list do not survive long enough to receive an orthotopic heart.

Guideline. Renal transplant for AL amyloidosis can be considered in very select patients.

Level of Evidence. V

Grade of Recommendation. C

Many of the reports of renal transplant for amyloidosis combine AL with AA amyloidosis, making outcomes for the former condition difficult to discern.[16] Options include cadaveric and living donor transplants. Given the limited cadaveric donor pool and the risk of recurrence or death related to their underlying AL amyloidosis, most renal transplants have been performed with living donors. Five-year OS rates have ranged from 67% to 78% in carefully selected patients, once again favoring those with limited disease and tumor burden and those who receive highly effective chemotherapy, including ASCT. It is our current practice to offer renal allografting to patients with AL amyloidosis with end-stage renal

Mayo Clin Proc. ■ August 2015;90(8):1054-1081 ■ http://dx.doi.org/10.1016/j.mayocp.2015.06.009
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disease who have already achieved a CR, most typically after ASCT.

Guideline. Liver transplant for AL amyloidosis is not recommended.

Level of Evidence. V

Grade of Recommendation. C

Unlike hereditary amyloidosis, liver transplant is rarely performed for patients with AL amyloidosis.[16,194,195] Outcomes are poor, as illustrated by 1- and 5-year OS of 32% and 22%, respectively, in a series of 9 patients transplanted in the United Kingdom.

TREATING LOCALIZED AMYLOIDOSIS

The location of the amyloid is an important clue in recognizing the amyloid as being localized. The most frequent sites of localized amyloid are the respiratory tract, genitourinary tract, and skin.[13] Pulmonary amyloid can be subdivided into nodular, laryngeal/tracheobronchial, and diffuse interstitial. Only the third type represents a manifestation of systemic AL amyloidosis.[196,197] The nodular form of amyloid presents as solitary pulmonary nodules or multiple nodules. This does not represent the systemic form of AL amyloidosis.[198] These nodules are not calcified and often require resection to exclude a diagnosis of malignancy. The usual treatment for tracheobronchial AL amyloidosis is yttrium-aluminum-garnet laser resection of the tissue and, more recently, external beam radiation therapy.[199] Obstructive ureterovesicular amyloidosis is always localized. Patients present with hematuria or obstruction.[200] Surgery[201] and dimethylsulfoxide instillation[202] are the standard approaches.

FUTURE DIRECTIONS

There is unprecedented interest in AL amyloidosis, which has resulted in improved outcomes for these patients. Clearly, more work needs to be done, especially in the realms of earlier diagnosis, salvaging the 35% of patients who seem destined to die within the first 6 months of diagnosis, and more innovative therapies. Physicians caring for patients with AL amyloidosis have been borrowing and customizing therapies used for patients with MM with varying degrees of success. One of the biggest failings in the science of the treatment of AL amyloidosis is the paucity of prospective trials, especially phase 3 trials. There are exciting possibilities ahead, including the study of oral proteasome inhibitors, antibodies directed at CD38 or CS-1, and other novel therapies that are showing promise in patients with MM. There are 3 antibodies in clinical trials that attack the amyloid itself that may be paradigm shifting (clinicaltrials.gov Identifiers NCT01707264, NCT01777243, NCT02245867, and NCT02312206). The role of organ transplant or ventricular assist devices may hold promise as well.

Abbreviations and Acronyms: **AH** = amyloid heavy chain; **AL** = amyloid light chain; **ASCT** = autologous stem cell transplant; **ATTR** = amyloid transthyretin; **B-Dex** = bortezomib and dexamethasone; **BMDex** = bortezomib plus melphalan and dexamethasone; **BNP** = brain natriuretic peptide; **Bor** = bortezomib; **BP** = blood pressure; **CR** = complete response; **CRAB** = hypercalcemia, renal insufficiency, anemia, or bone disease; **CTD** = cyclophosphamide, thalidomide, and dexamethasone; **CyBorD** = cyclophosphamide, bortezomib, and dexamethasone; **Cycl** = cyclophosphamide; **Dex** = dexamethasone; **dFLC** = difference between involved and uninvolved serum immunoglobulin free light chain levels; **eGFR** = estimated glomerular filtration rate; **FISH** = fluorescent in situ hybridization; **FLC** = free light chain; **HSCT** = hematopoietic stem cell transplant; **Hs-Tnt** = high sensitivity troponin T; **IFN** = interferon; **ITT** = intention-to-treat; **IMiD** = immunomodulatory drug; **Len** = lenalidomide; **MDex** = melphalan and dexamethasone; **Mel** = melphalan; **MM** = multiple myeloma; **NT-proBNP** = N-terminal brain natriuretic peptide; **NYHA** = New York Heart Association; **OHR** = overall hematologic response; **OS** = overall survival; **PFS** = progression-free survival; **PR** = partial response; **PS** = performance status; **POM** = pomalidomide; **Rx** = treatment; **SCT** = stem cell transplant; **thal-dex** = thalidomide-dexamethasone; **TRM** = treatment-related mortality; **VAD** = vincristine, doxorubicin, and dexamethasone; **VBMCP** = vincristine, carmustine, melphalan, cyclophosphamide, prednisone; **Vd** = velcade and dexamethasone; **VGPR** = very good partial response

Grant Support: This work was supported in part by the Robert A. Kyle Hematologic Malignancies Program, the Jabbs Foundation, and the Predolin Foundation.

Potential Competing Interests: Dr Dispenzieri has received research support from Celgene, Millenium, Pfizer, Jannsen, and Alnylam. Dr Kumar as received research support from Celgene, Novartis, Onyx, Millennium, Sanofi, and Janssen. Dr Reeder has received research support from Celgene, Novartis, and Millennium. Dr Mikhael has received research support from Celgene, Onyx, Abbvie, and Sanofi. Dr Grogan has received research support from Pfizer; and consulting fees from Prothena. Dr Fonseca has a patent for the prognostication of multiple myeloma based on genetic categorization of the disease; has received consulting fees from Celgene, Genzyme, BMS, Bayer, Lilly,

Onyx, Binding Site, Novartis, Sanofi, Millennium, and AMGEN; has sponsored research from Onyx; and is a member of the scientific advisory board of Applied Biosciences. Dr Ailawadhi has received honoraria from Millennium and Amgen. Dr Bergsagel has received research support from Novartis and Constellation Pharmaceuticals; and consultant fees from Amgen, Janssen, Sanofi-Aventis, Mundipharma, and BMS. Dr Stewart has received research support from Celgene and Millennium Pharmaceuticals; and consulting fees from Novartis and Millennium Pharmaceuticals. Dr Gertz has received research support from ISIS and Prothena; and honoraria from Celgene, Millennium Pharmaceuticals, and Novartis.

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APPENDIX

Levels of Evidence and Grades of Evidence for Recommendations

Level	Type of evidence
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power)
II	Evidence obtained from ≥1 well-designed experimental study; randomized trials with high false-positive and false-negative errors (low power)
III	Evidence obtained from well-designed, quasi-experimental studies, such as nonrandomized, controlled single-group, pre-post, cohort, time, or matched case-control series
IV	Evidence from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples

Grade	Grade for recommendation
A	There is evidence of type I or consistent findings from multiple studies of types II, III, and IV
B	There is evidence of types II, III, and IV, and findings are generally consistent
C	There is evidence of types II, III, and IV, but findings are inconsistent
D	There is little or no systematic empirical evidence

REFERENCES

1. 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(7):1817-1822.
2. Sipe JD, Benson MD, Buxbaum JN, et al. Nomenclature 2014: amyloid fibril proteins and clinical classification of the amyloidosis. *Amyloid*. 2014;21(4):221-224.
3. Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril protein nomenclature: 2010 recommendations from the nomenclature committee of the International Society of Amyloidosis. *Amyloid*. 2010;17(3-4):101-104.
4. Vrana JA, Gamez JD, Theis JD, et al. A clinical test for the identification of amyloid proteins in biopsy specimens by a novel method based on laser microdissection and mass spectrometry [ASH abstract 1480]. *Blood*. 2007;110(11).
5. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR III, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry based proteomic analysis in clinical biopsy specimens. *Blood*. 2009;114(24):4957-4959.
6. Brambilla F, Lavatelli F, Di Silvestre D, et al. Reliable typing of systemic amyloidoses through proteomic analysis of subcutaneous adipose tissue. *Blood*. 2012;119(8):1844-1847.
7. Sakata N, Hoshii Y, Nakamura T, et al. Colocalization of apolipoprotein AI in various kinds of systemic amyloidosis. *J Histochem Cytochem*. 2005;53(2):237-242.
8. Mikhael JR, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. *Mayo Clin Proc*. 2013;88(4):360-376.
9. Ansell SM, Kyle RA, Reeder CB, et al. Diagnosis and management of Waldenstrom macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) guidelines. *Mayo Clin Proc*. 2010;85(9):824-833.
10. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol*. 1995;32(1):45-59.
11. Lachmann HJ, Booth DR, Booth SE, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. *N Engl J Med*. 2002;346(23):1786-1791.
12. Comenzo RL, Zhou P, Fleisher M, Clark B, Teruya-Feldstein J. Seeking confidence in the diagnosis of systemic AL (Ig light-chain) amyloidosis: patients can have both monoclonal gammopathies and hereditary amyloid proteins. *Blood*. 2006;107(9):3489-3491.
13. Biewend ML, Menke DM, Calamia KT. The spectrum of localized amyloidosis: a case series of 20 patients and review of the literature. *Amyloid*. 2006;13(3):135-142.
14. Hamidi Asl K, Liepnieks JJ, Nakamura M, Benson MD. Organ-specific (localized) synthesis of Ig light chain amyloid. *J Immunol*. 1999;162(9):5556-5560.
15. Paccalin M, Hachulla E, Cazalet C, et al. Localized amyloidosis: a survey of 35 French cases. *Amyloid*. 2005;12(4):239-245.
16. Dispenzieri A, Gertz MA, Buadi F. What do I need to know about immunoglobulin light chain (AL) amyloidosis? *Blood Rev*. 2012;26(4):137-154.
17. Katzmann JA, Kyle RA, Benson J, et al. Screening panels for detection of monoclonal gammopathies. *Clin Chem*. 2009;55(8):1517-1522.
18. 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(8):3378-3383.
19. Wechalekar AD, Wassef NL, Gibbs SDJ, et al. A new staging system for AL amyloidosis incorporating serum free light chains, cardiac troponin-T and NT-ProBNP [ASH abstract 2796]. *Blood*. 2009;114(22).
20. Kumar S, Dispenzieri A, Katzmann JA, et al. Serum immunoglobulin free light-chain measurement in primary amyloidosis: prognostic value and correlations with clinical features. *Blood*. 2010;116(24):5126-5129.
21. 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. *Br J Haematol*. 2003;122(1):78-84.
22. Sanchorawala V, Seldin DC, Magnani B, Skinner M, Wright DG. Serum free light-chain responses after

high-dose intravenous melphalan and autologous stem cell transplantation for AL (primary) amyloidosis. *Bone Marrow Transplant*. 2005;36(7):597-600.
23. Kyle RA, Bayrd ED. Amyloidosis: review of 236 cases. *Medicine*. 1975;54(4):271-299.
24. Bryce AH, Ketterling R, Gertz MA, et al. Association of translocation t(11;14) with survival in patients with light chain (AL) amyloidosis. *Haematologica*. 2009;94(3):380.
25. Bochtler T, Hegenbart U, Cremer FW, et al. Evaluation of the cytogenetic aberration pattern in amyloid light chain amyloidosis as compared with monoclonal gammopathy of undetermined significance reveals common pathways of karyotypic instability. *Blood*. 2008;111(9):4700-4705.
26. Dispenzieri A, Gertz MA, Kyle RA, et al. Prognostication of survival using cardiac troponins and N-terminal pro-brain natriuretic peptide in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. *Blood*. 2004;104(6):1881-1887.
27. 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(18):3751-3757.
28. Palladini G, Lavatelli F, Russo P, et al. Circulating amyloidogenic free light chains and serum N-terminal natriuretic peptide type B decrease simultaneously in association with improvement of survival in AL. *Blood*. 2006;107(10):3854-3858.
29. 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(3):369-373.
30. Ruberg FL, Appelbaum E, Davidoff R, et al. Diagnostic and prognostic utility of cardiovascular magnetic resonance imaging in light-chain cardiac amyloidosis. *Am J Cardiol*. 2009; 103(4):544-549.
31. Bellavia D, Abraham RS, Pellikka PA, et al. Utility of Doppler myocardial imaging, cardiac biomarkers, and clonal immunoglobulin genes to assess left ventricular performance and stratify risk following peripheral blood stem cell transplantation in patients with systemic light chain amyloidosis (AI). *J Am Soc Echocardiogr*. 2011;24(4):444-454.
32. Palladini G, Barassi A, Klersy C, et al. The combination of high-sensitivity cardiac troponin T (hs-cTnT) at presentation and changes in N-terminal natriuretic peptide type B (NT-proBNP) after chemotherapy best predicts survival in AL amyloidosis. *Blood*. 2010;116(18):3426-3430.
33. Kristen AV, Giannitsis E, Lehrke S, et al. Assessment of disease severity and outcome in patients with systemic light-chain amyloidosis by the high-sensitivity troponin T assay. *Blood*. 2010;116(14):2455-2461.
34. Dispenzieri A, Gertz MA, Kumar SK, et al. High sensitivity cardiac troponin T in patients with immunoglobulin light chain amyloidosis. *Heart*. 2014;100(5):383-388.
35. Wechalekar AD, Gillmore JD, Wassef N, Lachmann HJ, Whelan C, Hawkins PN. Abnormal N-terminal fragment of brain natriuretic peptide in patients with light chain amyloidosis without cardiac involvement at presentation is a risk factor for development of cardiac amyloidosis. *Haematologica*. 2011;96(7):1079-1080.
36. Wechalekar AD, Schonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. *Blood*. 2013;121(17): 3420-3427.
37. Gertz MA, Kyle RA. Hepatic amyloidosis: clinical appraisal in 77 patients. *Hepatology*. 1997;25(1):118-121.
38. Hayman SR, Lacy MQ, Kyle RA, Gertz MA. Primary systemic amyloidosis: a cause of malabsorption syndrome. *Am J Med*. 2001;111(7):535-540.
39. Park MA, Mueller PS, Kyle RA, Larson DR, Plevak MF, Gertz MA. Primary (AL) hepatic amyloidosis: clinical features and natural history in 98 patients. *Medicine (Baltimore)*. 2003;82(5):291-298.
40. Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. *Blood*. 2014;124(15):2325-2332.
41. Gertz MA, Comenzo R, Falk RH, 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(4):319-328.
42. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. *J Clin Oncol*. 2012; 30(36):4541-4549.
43. Gertz MA, Kyle RA. Amyloidosis: prognosis and treatment. *Semin Arthritis Rheum*. 1994;24(2):124-138.
44. Gertz MA, Lacy MQ, Dispenzieri A. Amyloidosis: recognition, confirmation, prognosis, and therapy. *Mayo Clin Proc*. 1999; 74(5):490-494.
45. Mollee PN, Wechalekar AD, Pereira DL, et al. Autologous stem cell transplantation in primary systemic amyloidosis: the impact of selection criteria on outcome. *Bone Marrow Transplant*. 2004;33(3):271-277.
46. 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(10):1415-1418.
47. Cibeira MT, Sanchorawala V, Seldin DC, 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(16):4346-4352.
48. 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(8):2936-2938.
49. Skinner M, Sanchorawala 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(2):85-93.
50. Merlini G, Comenzo RL, Seldin DC, Wechalekar A, Gertz MA. Immunoglobulin light chain amyloidosis. *Expert Rev Hematol*. 2014;7(1):143-156.
51. 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(1):12-18.
52. Warsame R, Bang SM, Kumar SK, et al. Outcomes and treatments of patients with immunoglobulin light chain amyloidosis who progress or relapse postautologous stem cell transplant. *Eur J Haematol*. 2014;92(6):485-490.
53. Kyle RA, Greipp PR, O'Fallon WM. Primary systemic amyloidosis: multivariate analysis for prognostic factors in 168 cases. *Blood*. 1986;68(1):220-224.
54. Dingli D, Tan TS, Kumar SK, et al. Stem cell transplantation in patients with autonomic neuropathy due to primary (AL) amyloidosis. *Neurology*. 2010;74(11):913-918.
55. 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(9):989-995.
56. Gertz M, Lacy M, Dispenzieri A, et al. Troponin T level as an exclusion criterion for stem cell transplantation in light-chain amyloidosis. *Leuk Lymphoma*. 2008;49(1):36-41.
57. Gertz MA, Lacy MQ, Dispenzieri A, et al. Refinement in patient selection to reduce treatment-related mortality from autologous stem cell transplantation in amyloidosis. *Bone Marrow Transplant*. 2013;48(4):557-561.
58. Jaffe AS. The 10 commandments of troponin, with special reference to high sensitivity assays. *Heart*. 2011;97(11): 940-946.

59. Park HJ, Baek SH, Jang SW, et al. Direct comparison of B-type natriuretic peptide and N-terminal pro-BNP for assessment of cardiac function in a large population of symptomatic patients. *Int J Cardiol*. 2010;140(3):336-343.
60. Tagore R, Ling LH, Yang H, Daw HY, Chan YH, Sethi SK. Natriuretic peptides in chronic kidney disease. *Clin J Am Soc Nephrol*. 2008;3(6):1644-1651.
61. Palladini G, Foli A, Milani P, et al. Best use of cardiac biomarkers in patients with AL amyloidosis and renal failure. *Am J Hematol*. 2012;87(5):465-471.
62. Kourelis TV, Kumar SK, Gertz MA, et al. Coexistent multiple myeloma or increased bone marrow plasma cells define equally high-risk populations in patients with immunoglobulin light chain amyloidosis. *J Clin Oncol*. 2013;31(34):4319-4324.
63. Bochtler T, Hegenbart U, Kunz C, et al. Gain of chromosome 1q21 is an independent adverse prognostic factor in light chain amyloidosis patients treated with melphalan/dexamethasone. *Amyloid*. 2014;21(1):9-17.
64. Warsame R, Kumar SK, Gertz MA, et al. Abnormal FISH in patients with immunoglobulin light chain (AL) amyloidosis 2 is a risk factor for cardiac involvement and for death. *Blood Cancer J*. 2015;5:e310.
65. Kaufman GP, Dispenzieri A, Gertz MA, et al. Kinetics of organ response and survival following normalization of the serum free light chain ratio in AL amyloidosis. *Am J Hematol*. 2015; 90(3):181-186.
66. Trinkaus-Randall V, Walsh MT, Steeves S, Monis G, Connors LH, Skinner M. Cellular response of cardiac fibroblasts to amyloidogenic light chains. *Am J Pathol*. 2005;166(1):197-208.
67. Mishra S, Guan J, Plovie E, et al. Human amyloidogenic light chain proteins result in cardiac dysfunction, cell death, and early mortality in zebrafish. *Am J Physiol Heart Circ Physiol*. 2013;305(1):H95-H103.
68. Pepys MB, Herbert J, Hutchinson WL, et al. Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. *Nature*. 2002;417(6886): 254-259.
69. Bodin K, Ellmerich S, Kahan MC, et al. Antibodies to human serum amyloid P component eliminate visceral amyloid deposits. *Nature*. 2010;468(7320):93-97.
70. Wall JS, Kennel SJ, Stuckey AC, et al. Radioimmunodetection of amyloid deposits in patients with AL amyloidosis. *Blood*. 2010;116(13):2241-2244.
71. Dispenzieri A, Dingli D, Kumar SK, et al. Discordance between serum cardiac biomarker and immunoglobulin-free light-chain response in patients with immunoglobulin light-chain amyloidosis treated with immune modulatory drugs. *Am J Hematol*. 2010;85(10):757-759.
72. Gertz MA, Lacy MQ, Lust JA, Greipp PR, Witzig TE, Kyle RA. Long-term risk of myelodysplasia in melphalan-treated patients with immunoglobulin light-chain amyloidosis. *Haematologica*. 2008;93(9):1402-1406.
73. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med*. 2007;357(11):1083-1093.
74. Sanchorawala V, Skinner M, Quillen K, Finn KT, Doros G, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. *Blood*. 2007;110(10):3561-3563.
75. Palladini G, Russo P, Nuvolone M, et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. *Blood*. 2007;110(2):787-788.
76. Perfetti V, Casarini S, Palladini G, et al. Analysis of V(λ)-J(λ) expression in plasma cells from primary (AL) amyloidosis and normal bone marrow identifies 3r (λIII) as a new amyloid-associated germline gene segment. *Blood*. 2002;100(3):948-953.
77. Stevens FJ, Weiss DT, Solomon A. Structural bases of light chain related pathology. In: Zanetti M, Capra JD, eds. *The Antibodies*, Vol. 5. Amsterdam, the Netherlands: Harwood Academic Publishers; 1999:175-208.
78. Hurle MR, Helms LR, Li L, Chan W, Wetzel R. A role for destabilizing amino acid replacements in light-chain amyloidosis. *Proc Natl Acad Sci U S A*. 1994;91(12):5446-5450.
79. Stevens PW, Raffen R, Hanson DK, et al. Recombinant immunoglobulin variable domains generated from synthetic genes provide a system for in vitro characterization of light-chain amyloid proteins. *Protein Sci*. 1995;4(3):421-432.
80. Connors LH, Jiang Y, Budnik M, et al. Heterogeneity in primary structure, post-translational modifications, and germline gene usage of nine full-length amyloidogenic kappa1 immunoglobulin light chains. *Biochemistry*. 2007;46(49): 14259-14271.
81. Randles EG, Thompson JR, Martin DJ, Ramirez-Alvarado M. Structural alterations within native amyloidogenic immunoglobulin light chains. *J Mol Biol*. 2009;389(1):199-210.
82. Poshusta TL, Sikkink LA, Leung N, Clark RJ, Dispenzieri A, Ramirez-Alvarado M. Mutations in specific structural regions of immunoglobulin light chains are associated with free light chain levels in patients with Al amyloidosis. *PLoS One*. 2009; 4(4):e5169.
83. Kyle RA, Greipp PR. Primary systemic amyloidosis: comparison of melphalan and prednisone versus placebo. *Blood*. 1978;52(4):818-827.
84. Kyle RA, Greipp PR, Garton JP, Gertz MA. Primary systemic amyloidosis: comparison of melphalan/prednisone versus colchicine. *Am J Med*. 1985;79(6):708-716.
85. 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(17):1202-1207.
86. 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(3):290-298.
87. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. *Blood*. 2002;99(12): 4276-4282.
88. Gertz MA, Lacy MQ, Dispenzieri A, Hayman SR, Kumar S. Transplantation for amyloidosis. *Curr Opin Oncol*. 2007;19(2): 136-141.
89. Vesole DH, Perez WS, Akasheh M, Boudreau C, Reece DE, Bredeson CN. High-dose therapy and autologous hematopoietic stem cell transplantation for patients with primary systemic amyloidosis: a Center for International Blood and Marrow Transplant Research study. *Mayo Clin Proc*. 2006; 81(7):880-888.
90. D'Souza A, Dispenzieri A, Wirk B, et al. Improved outcomes after autologous hematopoietic cell transplantation for light chain amyloidosis: a Center for International Blood and Marrow Transplant Research study. *J Clin Oncol*. Submitted.
91. 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(4):766-769.
92. Goodman HJ, Gillmore JD, Lachmann HJ, Wechalekar AD, Bradwell AR, Hawkins PN. Outcome of autologous stem cell transplantation for AL amyloidosis in the UK. *Br J Haematol*. 2006;134(4):417-425.
93. Gertz MA, Blood E, Vesole DH, Abonour R, Lazarus HM, Greipp PR. A multicenter phase 2 trial of stem cell transplantation for immunoglobulin light-chain amyloidosis (E4A97): an Eastern Cooperative Oncology Group study. *Bone Marrow Transplant*. 2004;34(2):149-154.
94. Perz JB, Schonland SO, Hundemer M, et al. High-dose melphalan with autologous stem cell transplantation after VAD induction chemotherapy for treatment of amyloid light chain amyloidosis: a single centre prospective phase II study. *Br J Haematol*. 2004;127(5):543-551.
95. 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(12):1635-1643.
96. Cohen AD, Zhou P, Chou J, et al. Risk-adapted autologous stem cell transplantation with adjuvant dexamethasone +/- thalidomide for systemic light-chain amyloidosis: results of a phase II trial. *Br J Haematol*. 2007;139(2):224-233.
97. Landau H, Hassoun H, Rosenzweig MA, et al. Bortezomib and dexamethasone consolidation following risk-adapted melphalan and stem cell transplantation for patients with newly diagnosed light-chain amyloidosis. *Leukemia*. 2013; 27(4):823-828.
98. Kim SJ, Lee GY, Jang HR, et al. Autologous stem cell transplantation in light-chain amyloidosis patients: a single-center experience in Korea. *Amyloid*. 2013;20(4):204-211.
99. Dispenzieri A, Seenithamby K, Lacy MQ, 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;48(10):1302-1307.
100. Comenzo RL, Vosburgh E, Falk RH, et al. Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. *Blood*. 1998;91(10):3662-3670.
101. Dispenzieri A, Lacy MQ, Kyle RA, et al. Eligibility for hematopoietic stem-cell transplantation for primary systemic amyloidosis is a favorable prognostic factor for survival. *J Clin Oncol*. 2001;19(14):3350-3356.
102. Dispenzieri A, Kyle RA, Lacy MQ, et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. *Blood*. 2004;103(10):3960-3963.
103. Moreau P, Milpied N, de Faucal P, et al. High-dose melphalan and autologous bone marrow transplantation for systemic AL amyloidosis with cardiac involvement. *Blood*. 1996;87(7):3063-3064.
104. D'Souza A, Wirk B, Zhang MJ, et al. Improved outcomes of autologous hematopoietic cell transplantation (AHCT) for light chain (AL) amyloidosis: a Center for International Blood and Marrow Transplant Registry (CIBMTR) study. *Blood*. 2014; 124(21):193.
105. Fadia A, Casserly LF, Sanchorawala V, et al. Incidence and outcome of acute renal failure complicating autologous stem cell transplantation for AL amyloidosis. *Kidney Int*. 2003;63(5):1868-1873.
106. Gertz MA, Lacy MQ, Dispenzieri A, et al. Risk-adjusted manipulation of melphalan dose before stem cell transplantation in patients with amyloidosis is associated with a lower response rate. *Bone Marrow Transplant*. 2004;34(12):1025-1031.
107. Huang X, Wang Q, Jiang S, Chen W, Zeng C, Liu Z. The clinical features and outcomes of systemic AL amyloidosis: a cohort of 231 Chinese patients. *Clin Kidney J*. 2015;8(1):120-126.
108. Sanchorawala V, Brauneis D, Shelton AC, et al. Induction therapy with bortezomib followed by bortezomib-high dose melphalan and stem cell transplantation for AL amyloidosis: results of a prospective clinical trial [published online April 6, 2015]. *Biol Blood Marrow Transplant*. http://dx.doi.org/10.1016/j.bbmt.2015.04.001.
109. Sanchorawala V, Wright DG, Seldin DC, et al. High-dose intravenous melphalan and autologous stem cell transplantation as initial therapy or following two cycles of oral chemotherapy for the treatment of AL amyloidosis: results of a prospective randomized trial. *Bone Marrow Transplant*. 2004; 33(4):381-388.
110. Huang X, Wang Q, Chen W, et al. Induction therapy with bortezomib and dexamethasone followed by autologous stem cell transplantation versus autologous stem cell transplantation alone in the treatment of renal AL amyloidosis: a randomized controlled trial. *BMC Med*. 2014;12:2.
111. Sanchorawala V, Wright DG, Quillen K, et al. Tandem cycles of high-dose melphalan and autologous stem cell transplantation increases the response rate in AL amyloidosis. *Bone Marrow Transplant*. 2007;40(6):557-562.
112. Sanchorawala V, Hoering A, Seldin DC, et al. Modified high-dose melphalan and autologous SCT for AL amyloidosis or high-risk myeloma: analysis of SWOG trial S0115. *Bone Marrow Transplant*. 2013;48(12):1537-1542.
113. Guillaume B, Straetmans N, Jadoul M, Cosyns JP, Ferrant A. Allogeneic bone marrow transplantation for AL amyloidosis. *Bone Marrow Transplant*. 1997;20(10):907-908.
114. Gillmore JD, Davies J, Iqbal A, Madhoo S, Russell NH, Hawkins PN. Allogeneic bone marrow transplantation for systemic AL amyloidosis. *Br J Haematol*. 1998;100(1): 226-228.
115. Schonland SO, Lokhorst H, Buzyn A, et al. Allogeneic and syngeneic hematopoietic cell transplantation in patients with amyloid light-chain amyloidosis: a report from the European Group for Blood and Marrow Transplantation. *Blood*. 2006; 107(6):2578-2584.
116. Casserly LF, Fadia A, Sanchorawala V, et al. High-dose intravenous melphalan with autologous stem cell transplantation in AL amyloidosis-associated end-stage renal disease. *Kidney Int*. 2003;63(3):1051-1057.
117. Gertz MA, Buadi FK, Hayman SR. IgM amyloidosis: clinical features in therapeutic outcomes. *Clin Lymphoma Myeloma Leuk*. 2011;11(1):146-148.
118. Sanchorawala V, Blanchard E, Seldin DC, O'Hara C, Skinner M, Wright DG. AL amyloidosis associated with B-cell lymphoproliferative disorders: frequency and treatment outcomes. *Am J Hematol*. 2006;81(9):692-695.
119. Gono T, Matsuda M, Shimojima Y, et al. IgM AL amyloidosis due to B cell lymphoproliferative disorder: efficacy of high-dose melphalan followed by autologous stem cell transplantation. *Amyloid*. 2004;11(2):130-135.
120. Gertz MA, Lacy MQ, Lust JA, Greipp PR, Witzig TE, Kyle RA. Prospective randomized trial of melphalan and prednisone versus vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of primary systemic amyloidosis. *J Clin Oncol*. 1999;17(1):262-267.
121. Gertz MA, Lacy MQ, Lust JA, Greipp PR, Witzig TE, Kyle RA. Phase II trial of high-dose dexamethasone for previously treated immunoglobulin light-chain amyloidosis. *Am J Hematol*. 1999;61(2):115-119.
122. Gertz MA, Lacy MQ, Lust JA, Greipp PR, Witzig TE, Kyle RA. Phase II trial of high-dose dexamethasone for untreated patients with primary systemic amyloidosis. *Med Oncol*. 1999; 16(2):104-109.
123. Palladini G, Anesi E, Perfetti V, et al. A modified high-dose dexamethasone regimen for primary systemic (AL) amyloidosis. *Br J Haematol*. Jun 2001;113(4):1044-1046.
124. Dhodapkar MV, Hussein MA, Rasmussen E, et al. Clinical efficacy of high-dose dexamethasone with maintenance dexamethasone/alpha interferon in patients with primary systemic amyloidosis: results of United States Intergroup Trial Southwest Oncology Group (SWOG) S9628. *Blood*. 2004; 104(12):3520-3526.
125. Levy Y, Belghiti-Deprez D, Sobel A. Treatment of AL amyloidosis without myeloma [in French]. *Ann Med Interne (Paris)*. 1988;139(3):190-193.
126. Wardley AM, Jayson GC, Goldsmith DJ, Venning MC, Ackrill P, Scarffe JH. The treatment of nephrotic syndrome caused by primary (light chain) amyloid with vincristine, doxorubicin and dexamethasone. *Br J Cancer*. 1998;78(6):774-776.
127. van Gameren I, Hazenberg BP, Jager PL, Smit JW, Vellenga E. AL amyloidosis treated with induction chemotherapy with VAD followed by high dose melphalan and autologous stem cell transplantation. *Amyloid*. 2002;9(3):165-174.
128. Ichida M, Imagawa S, Ohmine K, et al. Successful treatment of multiple myeloma—associated amyloidosis by interferon-α,

dimethyl sulfoxide, and VAD (vincristine, adriamycin, and dexamethasone). *Int J Hematol*. 2000;72(4):491-493.
129. Gono T, Matsuda M, Shimojima Y, et al. VAD with or without subsequent high-dose melphalan followed by autologous stem cell support in AL amyloidosis: Japanese experience and criteria for patient selection. *Amyloid*. 2004;11(4):245-256.
130. Palladini G, Milani P, Foli A, et al. Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach. *Haematologica*. 2014;99(4):743-750.
131. Dietrich S, Schonland SO, Benner A, et al. Treatment with intravenous melphalan and dexamethasone is not able to overcome the poor prognosis of patients with newly diagnosed systemic light chain amyloidosis and severe cardiac involvement. *Blood*. 2010;116(4):522-528.
132. Sanchorawala V, Seldin DC, Berk JL, Sloan JM, Doros G, Skinner M. Oral cyclic melphalan and dexamethasone for patients with AL amyloidosis. *Clin Lymphoma Myeloma Leuk*. 2010;10(6):469-472.
133. Gertz MA, Kyle RA, Greipp PR. Response rates and survival in primary systemic amyloidosis. *Blood*. 1991;77(2):257-262.
134. Gertz MA, Kyle RA. Acute leukemia and cytogenetic abnormalities complicating melphalan treatment of primary systemic amyloidosis. *Arch Intern Med*. 1990;150(3):629-633.
135. Seldin DC, Choufani EB, Dember LM, et al. Tolerability and efficacy of thalidomide for the treatment of patients with light chain-associated (AL) amyloidosis. *Clin Lymphoma*. 2003;3(4):241-246.
136. Dispenzieri A, Lacy MQ, Geyer SM, et al. Low dose single agent thalidomide is tolerated in patients with primary systemic amyloidosis, but responses are limited [ASH abstract 4920]. *Blood*. 2004;104(11).
137. Dispenzieri A, Lacy MQ, Rajkumar SV, et al. Poor tolerance to high doses of thalidomide in patients with primary systemic amyloidosis. *Amyloid*. 2003;10(4):257-261.
138. Palladini G, Perfetti V, Perlini S, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). *Blood*. 2005;105(7):2949-2951.
139. Wechalekar AD, Goodman HJ, Lachmann HJ, Offer M, Hawkins PN, Gillmore JD. Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood*. 2007;109(2):457-464.
140. Gillmore J, Cocks K, Gibbs SDJ, et al. Cyclophosphamide, thalidomide and dexamethasone (CTD) versus melphalan plus dexamethasone (MD) for newly-diagnosed systemic AL amyloidosis: results from the UK Amyloidosis Treatment Trial [ASH abstract 2869]. *Blood*. 2009;114(22).
141. Palladini G, Russo P, Lavatelli F, et al. Treatment of patients with advanced cardiac AL amyloidosis with oral melphalan, dexamethasone, and thalidomide. *Ann Hematol*. 2009;88(4):347-350.
142. Dispenzieri A, Lacy MQ, Zeldenrust SR, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. *Blood*. 2007;109(2):465-470.
143. Sanchorawala V, Wright DG, Rosenzweig M, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. *Blood*. 2007;109(2):492-496.
144. Palladini G, Russo P, Foli A, et al. Salvage therapy with lenalidomide and dexamethasone in patients with advanced AL amyloidosis refractory to melphalan, bortezomib, and thalidomide. *Ann Hematol*. 2012;91(1):89-92.
145. Gibbs SDJ, De Cruz M, Sattianayagam PT, et al. Transient post chemotherapy rise in NT pro-BNP in AL amyloidosis: implications for organ response assessment [ASH abstract 1791]. *Blood*. 2009;114(22).
146. Tapan U, Seldin DC, Finn KT, et al. Increases in B-type natriuretic peptide (BNP) during treatment with lenalidomide in AL amyloidosis. *Blood*. 2010;116(23):5071-5072.
147. Specter R, Sanchorawala V, Seldin DC, et al. Kidney dysfunction during lenalidomide treatment for AL amyloidosis. *Nephrol Dial Transplant*. 2011;26(3):881-886.
148. 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(23):4777-4782.
149. Dinner S, Witteles W, Afghahi A, et al. Lenalidomide, melphalan and dexamethasone in an immunoglobulin light chain amyloidosis patient population with high rates of advanced cardiac involvement. *Haematologica*. 2013;98(10):1593-1599.
150. Sanchorawala V, Patel JM, Sloan JM, Shelton AC, Zeldis JB, Seldin DC. Melphalan, lenalidomide and dexamethasone for the treatment of immunoglobulin light chain amyloidosis: results of a phase II trial. *Haematologica*. 2013;98(5):789-792.
151. Palladini G, Russo P, Milani P, et al. A phase II trial of cyclophosphamide, lenalidomide and dexamethasone in previously treated patients with AL amyloidosis. *Haematologica*. 2013;98(3):433-436.
152. 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(21):4860-4867.
153. Kastritis E, Terpos E, Roussou M, et al. A phase 1/2 study of lenalidomide with low-dose oral cyclophosphamide and low-dose dexamethasone (RdC) in AL amyloidosis. *Blood*. 2012;119(23):5384-5390.
154. Dispenzieri A, Buadi F, Laumann K, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. *Blood*. 2012;119(23):5397-5404.
155. Kastritis E, Leleu X, Arnulf B, et al. A randomized phase III trial of melphalan and dexamethasone (MDex) versus bortezomib, melphalan and dexamethasone (BMDex) for untreated patients with AL amyloidosis. *Blood*. 2014;124(21):35.
156. Reece DE, Hegenbart U, Sanchorawala 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(4):865-873.
157. Reece DE, Sanchorawala V, Hegenbart U, et al. Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of a phase 1 dose-escalation study. *Blood*. 2009;114(8):1489-1497.
158. Reece DE, Hegenbart U, Sanchorawala V, et al. Long-term follow-up from a phase 1/2 study of single-agent bortezomib in relapsed systemic AL amyloidosis. *Blood*. 2014;124(16):2498-2506.
159. Palladini G, Foli A, Russo P, et al. Treatment of IgM-associated AL amyloidosis with the combination of rituximab, bortezomib, and dexamethasone. *Clin Lymphoma Myeloma Leuk*. 2011;11(1):143-145.
160. Gasparetto C, Sanchorawala V, Snyder RM, et al. Use of melphalan (M)/dexamethasone (D)/bortezomib in AL amyloidosis [ASCO abstract 8024]. *J Clin Oncol*. 2010;28(15 [suppl]).
161. Kastritis E, Wechalekar AD, Dimopoulos MA, et al. Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis. *J Clin Oncol*. 2010;28(6):1031-1037.
162. Lamm W, Willenbacher W, Lang A, et al. Efficacy of the combination of bortezomib and dexamethasone in systemic AL amyloidosis. *Ann Hematol*. 2011;90(2):201-206.
163. Palladini G, Milani P, Foli A, et al. Melphalan and dexamethasone with or without bortezomib in newly diagnosed AL amyloidosis: a matched case-control study on 174 patients. *Leukemia*. 2014;28(12):2311-2316.
164. Venner CP, Gillmore JD, Sachchithanantham S, et al. A matched comparison of cyclophosphamide, bortezomib and dexamethasone (CVD) versus risk-adapted cyclophosphamide, thalidomide and dexamethasone (CTD) in AL amyloidosis. *Leukemia*. 2014;28(12):2304-2310.

165. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. *Blood*. 2012;119(19):4391-4394.
166. 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(19):4387-4390.
167. Palladini G, Palladini G, Sachchithanantham S, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis [published online May 18, 2015]. *Blood*. http://dx.doi.org/10.1182/blood-2015-01-620302.
168. Lee JY, Lim SH, Kim SJ, et al. Bortezomib, melphalan, and prednisolone combination chemotherapy for newly diagnosed light chain (AL) amyloidosis. *Amyloid*. 2014;21(4):261-266.
169. Jaccard A, Comenzo RL, Hari P, et al. Efficacy of bortezomib, cyclophosphamide and dexamethasone in treatment-naive patients with high-risk cardiac AL amyloidosis (Mayo Clinic stage III). *Haematologica*. 2014;99(9):1479-1485.
170. Gertz MA, Kyle RA. Amyloidosis with IgM monoclonal gammopathies. *Semin Oncol*. 2003;30(2):325-328.
171. Wechalekar AD, Lachmann HJ, Goodman HJ, Bradwell A, Hawkins PN, Gillmore JD. AL amyloidosis associated with IgM paraproteinemia: clinical profile and treatment outcome. *Blood*. 2008;112(10):4009-4016.
172. Kikukawa Y, Yuki H, Hirata S, et al. Combined use of bortezomib, cyclophosphamide, and dexamethasone induces favorable hematological and organ responses in Japanese patients with amyloid light-chain amyloidosis: a single-institution retrospective study. *Int J Hematol*. 2015;101(2):133-139.
173. Berk JL, Keane J, Seldin DC, et al. Persistent pleural effusions in primary systemic amyloidosis: etiology and prognosis. *Chest*. 2003;124(3):969-977.
174. Dubrey S, Pollak A, Skinner M, Falk RH. Atrial thrombi occurring during sinus rhythm in cardiac amyloidosis: evidence for atrial electromechanical dissociation. *Br Heart J*. 1995;74(5):541-544.
175. Feng D, Syed IS, Martinez M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation*. 2009;119(18):2490-2497.
176. Rubinow A, Skinner M, Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. *Circulation*. 1981;63(6):1285-1288.
177. Gertz MA, Falk RH, Skinner M, Cohen AS, Kyle RA. Worsening of congestive heart failure in amyloid heart disease treated by calcium channel-blocking agents. *Am J Cardiol*. 1985;55(13, pt 1):1645.
178. Palladini G, Malamani G, Co F, et al. Holter monitoring in AL amyloidosis: prognostic implications. *Pacing Clin Electrophysiol*. 2001;24(8, pt 1):1228-1233.
179. 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(2):235-240.
180. Lin G, Dispenzieri A, Brady PA. Successful termination of a ventricular arrhythmia by implantable cardioverter defibrillator therapy in a patient with cardiac amyloidosis: insight into mechanisms of sudden death. *Eur Heart J*. 2010;31(12):1538.
181. Dhoble A, Khasnis A, Olomu A, Thakur R. Cardiac amyloidosis treated with an implantable cardioverter defibrillator and subcutaneous array lead system: report of a case and literature review. *Clin Cardiol*. 2009;32(8):E63-E65.
182. Yaoita H, Iwai-Takano M, Ogawa K, et al. Attenuation of diastolic heart failure and life-threatening ventricular tachyarrhythmia after peripheral blood stem cell transplantation combined with cardioverter-defibrillator implantation in myeloma-associated cardiac amyloidosis. *Circ J*. 2008;72(2):331-334.
183. Lin G, Dispenzieri A, Kyle R, Grogan M, Brady PA. Implantable cardioverter defibrillators in patients with cardiac amyloidosis. *J Cardiovasc Electrophysiol*. 2013;24(7):793-798.
184. Sayed RH, Rogers D, Khan F, et al. A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis. *Eur Heart J*. 2015;36(18):1098-1105.
185. Pinney JH, Lachmann HJ, Bansi L, et al. Outcome in renal Al amyloidosis after chemotherapy. *J Clin Oncol*. 2011;29(6):674-681.
186. Singer W, Sandroni P, Opfer-Gehrking TL, et al. Pyridostigmine treatment trial in neurogenic orthostatic hypotension. *Arch Neurol*. 2006;63(4):513-518.
187. Kumar SK, Dispenzieri A, Lacy MQ, et al. Doxycycline used as post transplant antibacterial prophylaxis improves survival in patients with light chain amyloidosis undergoing autologous stem cell transplantation [ASH abstract 3138]. *Blood*. 2012;120(21).
188. Wechalekar A, Whelan C, Sachchithanantham S, et al. A matched case control study of doxycycline added to chemotherapy for reducing early mortality in patients with advanced cardiac AL amyloidosis from the Alchemy Study Cohort [ASH abstract 3485]. *Blood*. 2014;124(21).
189. Cardoso I, Saraiva MJ. Doxycycline disrupts transthyretin amyloid: evidence from studies in a FAP transgenic mice model. *Faseb J*. 2006;20(2):234-239.
190. Ward JE, Ren R, Toraldo G, et al. Doxycycline reduces fibril formation in a transgenic mouse model of AL amyloidosis. *Blood*. 2011;118(25):6610-6617.
191. Obici L, Cortese A, Lozza A, et al. Doxycycline plus tauroursodeoxycholic acid for transthyretin amyloidosis: a phase II study. *Amyloid*. 2012;19(suppl 1):34-36.
192. Kumar SK, Dispenzieri A, Lacy MQ, et al. Doxycycline used as post transplant antibacterial prophylaxis improves survival in patients with light chain amyloidosis undergoing autologous stem cell transplantation. *ASH Annual Meeting Abstracts*. 2012. https://ash.confex.com/ash/2012/webprogram/Paper53022.html. Accessed July 7, 2015.
193. Wechalekar A. A matched case control study of doxycycline added to chemotherapy for reducing early mortality in patients with advanced cardiac AL amyloidosis from the Alchemy Study Cohort. *Blood*. 2014;124(21):3485.
194. Sattianayagam PT, Gibbs SD, Pinney JH, et al. Solid organ transplantation in AL amyloidosis. *Am J Transplant*. 2010;10(9):2124-2131.
195. Nowak G, Westermark P, Wernerson A, Herlenius G, Sletten K, Ericzon BG. Liver transplantation as rescue treatment in a patient with primary AL kappa amyloidosis. *Transpl Int*. 2000;13(2):92-97.
196. Utz JP, Gertz MA, Kalra S. External-beam radiation therapy in the treatment of diffuse tracheobronchial amyloidosis. *Chest*. 2001;120(5):1735-1738.
197. Pitz MW, Gibson IW, Johnston JB. Isolated pulmonary amyloidosis: case report and review of the literature. *Am J Hematol*. 2006;81(3):212-213.
198. Dundore PA, Aisner SC, Templeton PA, Krasna MJ, White CS, Seidman JD. Nodular pulmonary amyloidosis: diagnosis by fine-needle aspiration cytology and a review of the literature. *Diagn Cytopathol*. 1993;9(5):562-564.
199. Neben-Wittich MA, Foote RL, Kalra S. External beam radiation therapy for tracheobronchial amyloidosis. *Chest*. 2007;132(1):262-267.
200. Mariani AJ, Barrett DM, Kurtz SB, Kyle RA. Bilateral localized amyloidosis of the ureter presenting with anuria. *J Urol*. 1978;120(6):757-759.
201. Shittu OB, Weston PM. Localised amyloidosis of the urinary bladder: a case report and review of treatment. *West Afr J Med*. 1994;13(4):252-253.
202. Malek RS, Wahner-Roedler DL, Gertz MA, Kyle RA. Primary localized amyloidosis of the bladder: experience with dimethyl sulfoxide therapy. *J Urol*. 2002;168(3):1018-1020.