Treatment of AL Amyloidosis: Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Statement 2020 Update

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Abstract

Immunoglobulin light chain (AL) amyloidosis is a clonal plasma cell disorder leading to progressive and life-threatening organ failure. The heart and the kidneys are the most commonly involved organs, but almost any organ can be involved. Because of the nonspecific presentation, diagnosis delay is common, and many patients are diagnosed with advanced organ failure. In the era of effective therapies and improved outcomes for patients with AL amyloidosis, the importance of early recognition is further enhanced as the ability to reverse organ dysfunction is limited in those with a profound organ failure. As AL amyloidosis is an uncommon disorder and given patients' frailty and high early death rate, management of this complex condition is challenging. The treatment of AL amyloidosis is based on various anti–plasma cell therapies. These therapies are borrowed and customized from the treatment of multiple myeloma, a more common disorder. However, a growing number of phase 2/3 studies dedicated to the AL amyloidosis population are being performed, making treatment decisions more evidence-based. Supportive care is an integral part of management of AL amyloidosis because of the inherent organ dysfunction, limiting the delivery of effective therapy. This extensive review brings an updated summary on the management of AL amyloidosis, sectioned into the 3 pillars for survival improvement: early disease recognition, anti–plasma cell therapy, and supportive care.

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Immunoglobulin light chain amyloidosis (AL amyloidosis) and immunoglobulin heavy chain amyloidosis (AH amyloidosis) are plasma cell disorders characterized by deposition of insoluble amyloid fibrils composed of immunoglobulin chains. Most of the literature to date refers to AL amyloidosis, the more common immunoglobulin-related type. As there is no evidence for a clear difference in clinical presentation, treatment, or prognosis between AL and AH amyloidosis, both types are referred to as AL amyloidosis.

AL amyloidosis is the most commonly diagnosed form of systemic amyloidosis,[1]

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with an incidence of approximately 1 case per 100,000 person-years.[2] Other forms of systemic amyloidosis are listed in Table 1.[3] Typing of the amyloid is imperative because treatment strategies are dependent on the identity of the precursor protein.[4,5] In the case of systemic AL amyloidosis, the precursor protein is bone marrow plasma cell–derived immunoglobulin light chains, and targeting the plasma cell clone is the mainstay of therapy.

In this article, we discuss the 3 fundamental pillars to improve survival in AL amyloidosis, namely, early disease recognition, anti–plasma cell therapy, and supportive care (Figure 1). These 3 pillars, when combined, enhance the likelihood of overcoming this life-threatening disorder and improving long-term survival.[6-8] Whereas the management of anti–plasma cell therapy is within the scope of hematology, both disease recognition and supportive care domains expand beyond the hematologist's reach. Therefore, efforts should be invested in improving disease recognition among the medical specialists who often encounter AL patients at symptom onset, including primary care physicians, cardiologists, nephrologists, neurologists, and gastroenterologists.[9] In addition, supportive care is best guided by the dominant involved organs and requires a multidisciplinary approach.

We present an extensive review of the literature with the aim of making recommendations within the context of the best evidence and expert opinion as we have done in the past for patients with AL amyloidosis,[10] multiple myeloma (MM),[11-13] and Waldenström macroglobulinemia.[14]

FIRST PILLAR: EARLY RECOGNITION

Recognizing amyloidosis is challenging, given the nonspecific symptoms and heterogeneity in presentation. The median time from symptom onset to diagnosis is approximately 6 to 12 months.[9,15-17] The initial barrier to diagnosis is the patient's self-interpretation of symptoms.[17] Once the patient seeks medical attention, the barrier to diagnosis becomes within the health care system, with an average of 3 or 4 different physicians visited before the diagnosis is established. During the journey to diagnosis, misdiagnosis is not uncommon and further contributes to diagnosis delay.[17] Notably, patients with renal involvement usually have a more straightforward pathway to diagnosis, and many are diagnosed within 6 months from symptom onset.[17] This may be explained by the routine use of kidney biopsy in patients with proteinuria.[18] Nonetheless, patients with heart involvement are those who are in the greatest need of early diagnosis to improve outcome.

Presentation and Organ Involvement

Fatigue is the most common symptom, reported by 80% of patients.[17] Other common symptoms include exertional dyspnea, peripheral edema, paresthesias, weight loss, purpura, dysgeusia, xerostomia, and macroglossia. The 2 most commonly involved organs are the heart and the kidneys; each exists in 60% to 80% of patients. Heart involvement is defined on the basis of typical echocardiographic findings, including thickened heart walls, restrictive filling pattern, sparkling appearance of the myocardium, and abnormal strain pattern with a base-to-apex gradient. Cardiac magnetic resonance can assist in clarifying heart involvement when echocardiographic findings are equivocal. The hallmark feature of cardiac amyloidosis on cardiac magnetic resonance is late gadolinium enhancement. Elevated soluble cardiac biomarkers, cardiac troponins and natriuretic peptides, are sensitive but not specific. Endomyocardial biopsy is rarely required to confirm heart involvement and should be mainly used when heart involvement is highly suspected but tissue diagnosis of amyloidosis from more accessible tissues is not successful. Renal involvement is defined as the presence of more than 0.5 g/24-hour nonselective proteinuria,[19] but more than half of the patients with renal AL

TABLE 1. Classification of the Most Common Amyloidoses

Type of amyloidosis	Precursor protein component	Clinical presentation
AL[a] (previously referred to as primary amyloidosis)	κ or λ immunoglobulin light chain	Systemic or localized; see text
AH	γ, μ, α, δ, ε immunoglobulin heavy chain	Systemic or localized; see text
ATTR		
Wild-type ATTR[b] (age-related amyloidosis)	Normal transthyretin	Restrictive cardiomyopathy; carpal tunnel syndrome Lumbar spinal stenosis Biceps tendon rupture
Variant ATTR[b] (also referred to as hereditary ATTR)	Mutant transthyretin	Polyneuropathy phenotype, cardiomyopathy phenotype, and mixed phenotype; leptomeningeal involvement; vitreous opacities
AA (previously referred to as secondary amyloidosis)	Serum amyloid A	Renal presentation most common; associated with chronic inflammatory conditions; underlying disease is typically acquired, but hereditary in case of familial periodic fever syndromes
ALECT2	Leukocyte chemotactic factor 2	Acquired; renal or liver presentation
Aβ2M	β_2-microglobulin	Acquired in patients on long-term dialysis; carpal tunnel syndrome, large joint arthropathy
AApoA-IV	Apolipoprotein A-IV	Acquired; renal or cardiac amyloidosis
Rare hereditary amyloidosis types		
AGel; also known as familial amyloidosis, Finnish type	Gelsolin	Triad of corneal lattice dystrophy, facial nerve paralysis, and cutis laxa
AFib	Fibrinogen α-chain	Usually renal presentation
ALys	Lysozyme	Sicca syndrome, renal dysfunction, liver or spleen rupture, gastrointestinal ulcers
AApoA-I	Apolipoprotein A-I	Mutation-dependent, can affect various organs
AApoA-II	Apolipoprotein A-II	Renal amyloidosis
AApoC-II	Apolipoprotein C-II	Renal amyloidosis
AApoC-III	Apolipoprotein C-III	Renal amyloidosis, sicca syndrome

[a]AL/AH amyloidosis is the only form of amyloidosis that is secondary to a clonal plasma cell disorder. AL amyloidosis can be associated with multiple myeloma or more rarely with other B-cell–secreting disorders.
[b]TTR refers to transthyretin, previously known as prealbumin.

amyloidosis present with nephrotic-range proteinuria.[20] Kidney involvement can be manifested with or without renal failure. Rarely, renal failure without proteinuria is seen in vascular-limited renal involvement.[21]

Other organ involvement is notable for peripheral neuropathy (symmetric painful neuropathy, numbness, imbalance), autonomic neuropathy (orthostatic hypotension, alteration in bowel movement, early satiety, erectile dysfunction, and urinary retention), liver (hepatomegaly or elevated serum alkaline phosphatase, jaundice, weight loss), gastrointestinal tract (diarrhea, constipation, malabsorption, weight loss, gastrointestinal bleeding), muscle (muscle weakness, myalgia, pseudohypertrophy, atrophy), joints (polyarthropathy), spleen (hyposplenism), lungs (dyspnea, cough, diffuse interstitial infiltrates on imaging), bleeding diathesis (deficiencies of clotting factors, such as factor X), and skin (alopecia, purpura). Vascular involvement can result in exercise-induced limb claudication or angina pectoris as well as in jaw claudication on chewing.

Given the wide organ involvement, review of systems at initial encounter is paramount to assess disease extent and to guide the diagnostic evaluation. As the most commonly involved organs are heart, kidneys, liver, and nerves, the minimal evaluation should include measurement of seated and standing blood pressure, N-terminal brain natriuretic peptide (NT-proBNP) or

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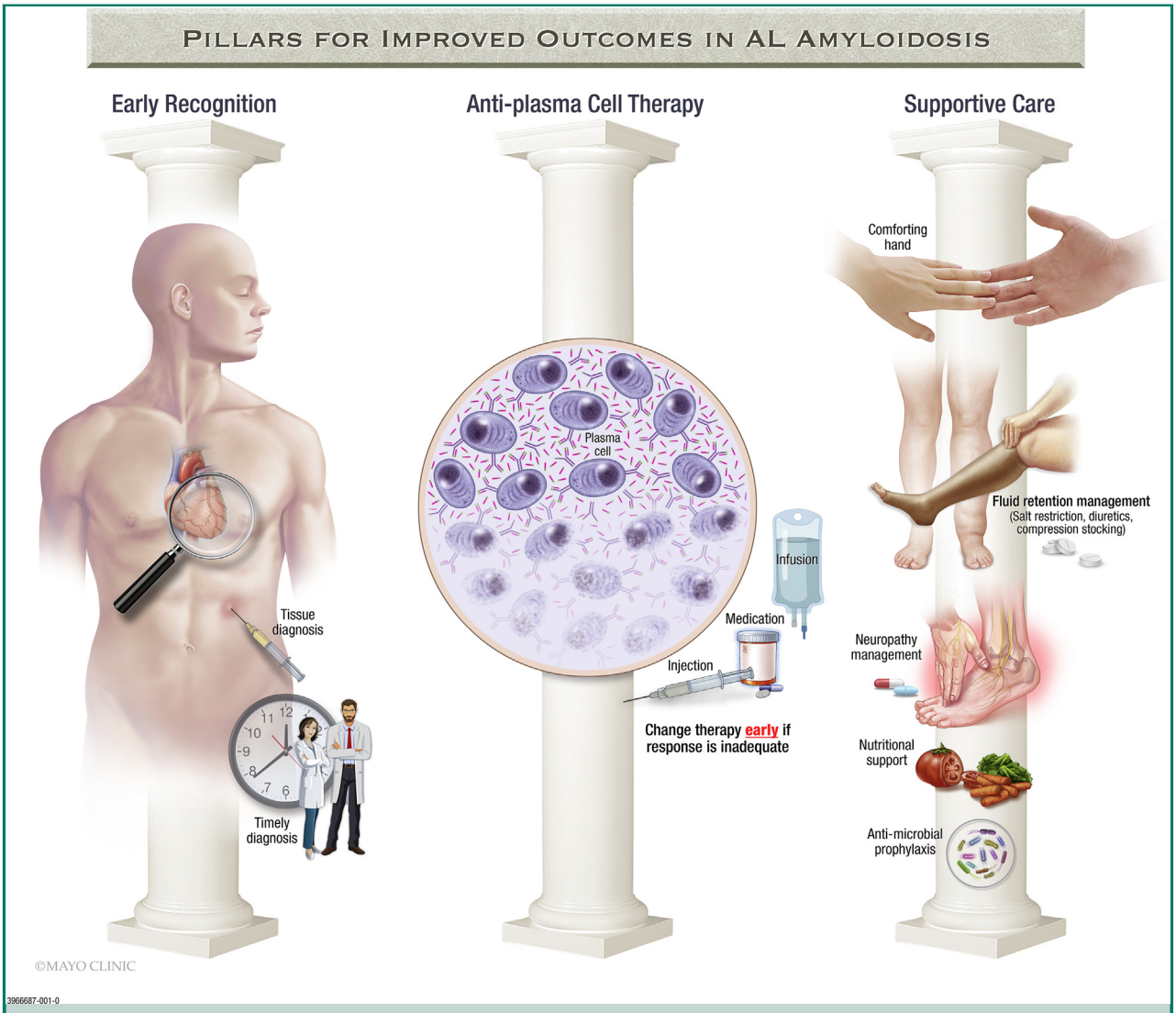

FIGURE 1. Three-pillar scheme for improved survival in AL amyloidosis.

brain natriuretic peptide, troponin T or troponin I, alkaline phosphatase, creatinine, and 24-hour urine protein.[22-30] Nerve conduction studies and electromyography aid in assessment of large-fiber peripheral neuropathy. Autonomic testing is appropriate on the basis of symptoms and should include evaluation of sweating and cardiovagal and adrenergic function as well as of gastric motility and bladder emptying.

Diagnosis of AL Amyloidosis

The diagnosis of amyloidosis relies on demonstration of amyloid deposits on a tissue sample. The tissue source can be the affected organ. However, a more accessible tissue, such as subcutaneous fat, should initially be pursued when suspicion for amyloidosis is raised. Fat aspiration combined with bone marrow biopsy (performed for assessment of the underlying plasma cell disorder) will yield the diagnosis in approximately 90% of patients.[18] For amyloid to be recognized, special staining is required. Congo red is the "gold standard" staining, but thioflavin T or sulfated alcian blue can also be used. Congo red staining under polarized light demonstrates apple-green birefringence, illustrating the highly organized ultrastructure of the amyloid fibrils.

Once a tissue diagnosis is established, the next step is to type the amyloid (ie, determine the precursor protein) as clinical manifestation, treatment, and prognosis are driven by the precursor protein. Several methods of typing are available. The gold standard technique is laser microdissection, followed by mass spectrometry–based proteomic analysis, which has high sensitivity and specificity.[1,5] Alternative typing methods include antigen-antibody–based analyses, such as immunofluorescence, immunohistochemistry, and immunogold.[31,32] However, antigen-antibody–based analyses have several limitations, including suboptimal specificity (due in part to cross-reactivity with deposited immunoglobulins), suboptimal sensitivity (due to bias toward common or suspected amyloid types), and potential for specimen depletion because a different tissue section is needed for each antibody tested. Mass spectrometry–based proteomics, in contrast, has high sensitivity and specificity, requires very little tissue, and unambiguously identifies all amyloid types in a single assay. A study reported that mass spectrometry–based proteomics is able to identify the amyloid type in 80% of amyloid specimens that could not be typed by immunohistochemistry.[33] It cannot be overemphasized that the presence of a monoclonal protein in a patient with amyloidosis does not prove AL type.[34-39]

Finally, the distinction between localized and systemic AL amyloidosis is required. The designation localized applies to AL amyloidosis in which the precursor protein is produced at the site of amyloid deposition and is typically not associated with a detectable circulating monoclonal protein in the serum or urine. The common sites of localized amyloidosis are the tracheobronchial tree, lungs, urinary tract, skin and soft tissue, oropharynx, gastrointestinal tract, and eyes.[40,41] At Mayo Clinic, approximately 7% of cases of AL amyloidosis are localized.[40]

Evaluation of Patients With AL Amyloidosis

Screening for a monoclonal protein (M-protein) is done by serum and urine electrophoresis/immunofixation studies and serum free light chain (FLC) assay.[42] More recently at Mayo Clinic, immunofixation has been replaced by the mass spectrometry method (Mass-Fix).[43] The Mass-Fix assay has the ability to detect M-proteins with light chain glycosylation, which has been reported to be a risk factor for progression of AL amyloidosis and other plasma cell disorders.[44] Despite the typical low clonal burden, at least 1 abnormality is found in virtually all patients.[20] In addition, bone marrow aspiration and biopsy and fluorescence in-situ hybridization (FISH) testing are indicated and can affect treatment decisions during the disease course. Rarely, other B-cell secretory diseases including Waldenström macroglobulinemia, chronic lymphocytic leukemia, and other non-Hodgkin lymphomas can be the underlying cause of AL amyloidosis.[45]

Prognosis of AL Amyloidosis

The prognosis of AL amyloidosis is dependent on the 2 compartments of the disease—organ involvement and the underlying plasma cell clone. The degree of heart involvement is the single most important predictor for short-term[46] and long-term[7] survival. The number of involved organs[20] and hepatic[47] and autonomic[48] involvement also influence survival. The plasma cell clone becomes relevant for long-term survival.[7,47]

Whereas improvement in survival was noted at Mayo Clinic and the UK National Amyloidosis Center during past decades,[49,50] the proportion of patients dying within 6 to 12 months of diagnosis remains fixed at approximately 30% to 45%, with the least improvement in survival noted for these sickest patients.[51] The high early death rate explains why newly diagnosed patients tend to fare worse than patients with relapsed or refractory AL[52] and why the risk factors for death are different during the first year and after the first year.[47] However, in recent years with the advent of effective therapies, the rate of early death has declined, marking an important step in improving outcome in this disease. In our institution, the 6-month death rate among newly diagnosed patients declined from

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37% before 2005 to 25% from 2005 onward.[46]

Cardiac Staging. Soluble cardiac biomarkers are the basis for cardiac staging. Given the profound impact of heart involvement on survival, the use of cardiac biomarkers for staging not only informs on the degree of heart involvement but also is prognostic. The advantage of blood tests for assessing cardiac status includes assay reproducibility, ease of testing, and relatively low cost. Disadvantages of the cardiac biomarkers include the number of assays available and the impact of renal failure on interpretation of the results.

The first cardiac model was the 2004 Mayo model, which incorporated troponin T and NT-proBNP into a 3-stage model (Table 2).[23] The stage 3 in this model was later subdivided into 2 substages (3a and 3b), using a higher cutoff of NT-proBNP.[53] This European modification of the Mayo 2004 model is successful in identifying high-risk patients for early death[54] as well as better performance in those with low estimated glomerular filtration rate (eGFR) and atrial arrhythmia.[55] Serum immunoglobulin FLCs are prognostic[56-58] and have been incorporated into the Mayo 2012 staging system.[59] We have provided a conversion tool between troponin T and high-sensitivity troponin T following the adoption of this assay by the Food and Drug Administration in 2017, making it widely available in the United States.[60] A conversion table for all cardiac biomarkers by the various cardiac models can be viewed in Table 3.

Echocardiographic parameters, such as ejection fraction, longitudinal left ventricular strain,[61] and stroke volume index,[62] are prognostic as well. However, they may be limited by variability in local expertise and imaging protocols.

Renal Staging. Palladini et al[29] introduced a model for prediction of the risk of progression to dialysis. The rationale for this staging system is driven by the fact that renal involvement does not markedly increase the risk of death, but advanced renal involvement increases the risk of dialysis dependence. This 3-stage model is based on an eGFR of less than 50 mL/min per 1.73 m^2 and 24-hour proteinuria of more than 5 g. When both were present at diagnosis, the risk for dialysis at 3 years was 60% and 85% in 2 separate cohorts, whereas not having any of these parameters yielded very low 3-year risk of progression to dialysis (0% and 4%, respectively).

Prognostic Impact of Serum Immunoglobulin FLCs. As mentioned before, serum immunoglobulin FLCs are prognostic. Immunoglobulin FLCs are also the main tool for assessing the hematologic response (HR),[63] as is discussed later, and thus they carry a significant impact on survival throughout the disease course.

Prognostic Impact of Plasma Cell Burden and Biology. The median bone marrow plasmacytosis is 10%.[46] Patients with more than 10% marrow plasmacytosis have a worse outcome than those with 10% or less marrow plasmacytosis.[64,65] We recently refined the independent worse outcome to patients with 20% or more bone marrow plasma cells.[66] These patients are more likely to have concomitant myeloma phenotype and high-risk FISH abnormalities, explaining in part the worse outcome in this group of patients. In contrast, the Boston University (BU) group did not find that more than 10% plasmacytosis had an impact on survival, but their analysis was restricted to patients undergoing autologous stem cell transplant (ASCT) with up to 30% plasmacytosis.[67]

Other plasma cell characteristics, like proliferative rate and FISH abnormalities, have also been reported to be prognostic. Translocation t(11;14) is associated with inferior survival of patients treated with bortezomib,[68-70] whereas trisomies[70,71] and del17p[72] are poor prognostic markers in AL amyloidosis.

SECOND PILLAR: ANTI–PLASMA CELL THERAPY

At present, the mainstay of treatment is targeting the underlying plasma cell clone. The

TABLE 2. Cardiac Risk Models in AL Amyloidosis[a]

	Troponin (μg/L)	NT-proBNP (ng/L)	Other	Stages[b]	Hazard ratio for death[c]
Mayo 2004 model[23,24,191-193]	≥0.035	≥332	—	1	Reference
				2	2.5 (1.9-3.5)
				3	6.7 (5.0-9.1)
European 2015 modification of Mayo 2004 model[53]	≥0.035	≥332	Stage 3 only: NT-proBNP >8500 ng/L	1	Reference
				2	2.5 (1.9-3.5)
				3[a]	4.9 (3.6-6.8)
				3[b]	11.1 (8.1-15.4)
Revised Mayo 2012 model[59]	≥0.025	≥1800	dFLC ≥180 mg/L	1	Reference
				2	1.7 (1.2-2.3)
				3	4.1 (3.1-5.5)
				4	6.3 (4.8-8.3)

[a]dFLC, difference between involved and uninvolved immunoglobulin free light chains; NT-proBNP, N-terminal brain natriuretic peptide.
[b]For each stage, stage 1 is absence of any risk factors; stage 2 is presence of 1 risk factor; stage 3 is presence of 2 risk factors; and where applicable, stage 4 is all risk factors present. The exception is the European 2015 modification of the Mayo 2004 model, in which stage 3 (2 risk factors) is further divided by whether NT-proBNP is >8500 ng/L.
[c]Data are derived from Supplemental Table 2 of reference number 54.

amyloid fibrils in the tissue and intermediate soluble fibrils are the source of tissue injury and dysfunction,[73,74] and by their elimination, organ recovery can take place. Another approach for therapy by targeting the amyloid deposits using monoclonal antibodies has been investigated in the past decade with several antibodies, but none has yet reached a regulatory approval stage.

Any recommendation for the treatment of AL is confounded by disease 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, makes these recommendations sound. Table 4 contains current HR and organ response (OR) criteria.[19,63] Clinical trials should always be considered the first choice when available. In the absence of clinical trials, recommendations are as discussed here. For each recommendation we assigned the level of evidence and its grade to indicate the quality of evidence the recommendations are based upon [for details see Box].

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

Level of Evidence: II

Grade of Recommendation: A

Guideline: The ideal goal is hematologic complete response (CR), but this has to be weighed against toxicity of therapy and lack of specificity and sensitivity of assays.

TABLE 3. Conversion Table for the Various Cardiac Biomarkers Used Across the 3 Cardiac Risk Models[a,b]

Model	Troponin T (μg/L)	Troponin I (μg/L)	High-sensitivity troponin T (ng/L)	NT-proBNP (ng/L)	BNP (ng/L)
Mayo 2004 model	≥0.035	≥0.1	≥50	≥332	≥81
European 2015 modification of Mayo 2004 model	≥0.035	≥0.1	≥50	≥332	≥81
				>8500	>700
Revised Mayo 2012 model	≥0.025	≥0.07	≥40	≥1800	≥400

[a]BNP, brain natriuretic peptide; NT-proBNP, N-terminal brain natriuretic peptide.
[b]Conversion data are obtained from original papers as well as by conversion tool between troponin T and high-sensitivity troponin T.[60]

Level of Evidence: III

Grade of Recommendation: B

Guideline: Patients who do not achieve at least partial response (PR) within 2 cycles or VGPR within 4 cycles of therapy or after ASCT should be offered an alternative therapy.

Level of Evidence: III

Grade of Recommendation: B

Guideline: Improvement in organ function, preferably to near-normal value, is the preferred organ response goal.

Level of Evidence: III

Grade of Recommendation: B

TABLE 4. AL Amyloidosis Hematologic and Organ Response Criteria

Response type	Criteria
Hematologic response[63]	
Complete response	Negative serum and urine immunofixation and normal serum immunoglobulin κ/λ FLC ratio
Very good partial response	dFLC <40 mg/L
Partial response	dFLC decrease of >50%
No response	Less than a partial response
Organ response[19,63]	
Cardiac response	Decrease of NT-proBNP by >30% and 300 ng/L (if baseline NT-proBNP >650 ng/L)
Renal response	At least 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
Hepatic response	50% decrease in abnormal alkaline phosphatase value or decrease in radiographic liver size by at least 2 cm

dFLC, difference between involved and uninvolved serum immunoglobulin free light chains (a value adequate to measure response is deemed to be 50 mg/L); eGFR, estimated glomerular filtration rate; FLC, free light chain; NT-proBNP, N-terminal brain natriuretic peptide.

Hematologic Response Goal

Our consensus recommendation is to aim for at least hematologic VGPR (difference between involved and uninvolved light chains [dFLC] <40 mg/L). Achievement of hematologic CR (negative serum and urine immunofixation and normal serum FLC ratio) is the optimal response category, but it can be safely achieved only in a subset of patients. As the survival difference between VGPR and CR is smaller compared with the survival difference between VGPR and PR (>50% reduction in dFLC),[63] VGPR or better is set as the realistic treatment goal, which can be achieved in 40% to 80% of the patients by modern therapies.[46,53,75] Nonetheless, we recommend referral of patients who achieved a VGPR but not a CR to an amyloidosis center to further assess the need for and feasibility of CR.

The importance of deep HR in AL can also be viewed from the perspective of light chain burden. Patients who achieved VGPR or CR and in whom the involved FLC (iFLC) serum level was 20 mg/L or less had superior OR, progression-free survival (PFS), and overall survival (OS) compared with those with CR or VGPR but with iFLC level of more than 20 mg/L. Similarly, the UK group reported that the achievement of dFLC below 10 mg/L at 6 months, irrespective of baseline dFLC, was associated with the best cardiac response rate, time to next therapy, and OS and was independent of CR or VGPR state.[75] We recently proposed a new definition for hematologic CR to include serum and urine immunofixation negativity plus iFLC level of 20 mg/L or less or dFLC of 10 mg/L or less, both of which were superior to the current CR definition.[76] This definition, however, has not been validated. Both the BU and the Pavia groups reported that the addition of iFLC level below 20 mg/L to the conventional definition of CR carries a survival advantage compared with CR alone.[77,78]

Whether long-term outcomes will differ according to the means of arriving at a hematologic CR is still a matter of debate. This is most notable in the context of ASCT vs standard-intensity therapies. For patients achieving hematologic CR after standard-intensity therapies, the 5-year OS is about 70%. For patients undergoing ASCT and who achieve a CR, 5-year survival rates approach 90%.[6,79] However, this survival gap is confounded by the fact that patients undergoing ASCT are selected and fit at baseline and thus more likely to survive long term.[7]

Timing of HR

The importance of the timing of the HR is best provided by the HR criteria.[63] These

criteria were assessed at 3 months and 6 months from therapy initiation, and it was found that CR or VGPR achievement as early as 3 months from therapy initiation translated into survival advantage over those who achieved less than VGPR. Because AL amyloidosis is typically diagnosed late when organ function is profoundly affected, early HR is critical to maximize organ recovery and survival. This is the basis for our recommendation to switch therapy if PR is not achieved after 2 cycles. Similarly, if VGPR is not achieved within 4 cycles, change to alternative therapy or therapy intensification (if feasible) is recommended.

The Role of Bone Marrow Minimal Residual Disease in Response Assessment

Assessment of marrow residual disease using immunohistochemistry is challenging, especially in low-burden disease such as AL amyloidosis. Multiparametric flow cytometry (MFC) has increasingly been used to assess minimal residual disease (MRD) in various hematologic malignant neoplasms. In AL amyloidosis, the use of MFC to assess MRD has been investigated in several studies, most of them from our group. The first study with 82 patients reported that low residual disease by MFC (<0.1%) is prognostic for PFS and OS.[80] Subsequent analysis of this study with a longer follow-up reported that lack of clonal marrow plasma cells by MFC is associated with improved PFS compared with patients with residual clonal plasma cells, particularly among patients who achieved a CR. We recently reported the results of MFC with a higher sensitivity of 1×10^{-5} or more among 44 patients.[81] MRD negativity was more likely to be achieved among those who received ASCT and in those who achieved a CR. The achievement of MRD negativity was associated with a longer PFS and higher likelihood of cardiac response. The Greek group reported on the clinical outcomes of 51 patients based on MRD status using next-generation flow cytometry.[82] In that study, patients with MRD-negative disease were more likely to achieve OR and less likely to experience hematologic relapse.

Organ Response Goals

The current OR criteria are based on reduction in organ parameter and are binary, that is, response vs no response (Table 4).[19] The likelihood of achieving OR and a longer survival is proportional to the depth of the HR.[63,75,83,84] New OR criteria, which are based on graded organ function improvement, are the focus of an international collaboration study. Preliminary results from that study confirm that deeper OR correlates with a longer survival.

The OR lags behind the HR. Organ response kinetics has been investigated among 414 patients who achieved OR to first-line therapy.[84] The median time from treatment initiation to heart, kidney, and liver response was 9, 6, and 6 months, respectively, whereas the median time to best organ function was 24, 29, and 35 months, respectively. These figures highlight the slow process of organ recovery, which requires regular organ function monitoring and provision of long-term supportive care.

Indications for Therapy in Newly Diagnosed AL

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 specifically addressed this point, but it is known through randomized trials that patients with AL treated with anti–plasma cell therapy live longer and can have clinical improvement compared with those who receive either no therapy or ineffective therapy like colchicine.[85-88] Those patients who have monoclonal gammopathy of undetermined significance or smoldering myeloma with an incidental finding of a positive Congo red reaction of the bone marrow do not require therapy and have low risk of progression to vital organ involvement. Such patients should be observed periodically with amyloid-directed review of systems, serum immunoglobulin FLCs, alkaline phosphatase,

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troponin, NT-proBNP, and creatinine as well as with spot urine for albumin.

Initial Therapy for Patients With Systemic AL Amyloidosis

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

Level of Evidence: III

Grade of Recommendation: B

In our routine practice, the first question asked is whether a patient is a candidate for high-dose chemotherapy followed by ASCT (Figure 2; Table 5). Among eligible patients, ASCT is an excellent option with potential for long-term survival. There are, however, no randomized trial data to support that it is superior therapy. On the contrary, a small phase 3 study concluded that ASCT is inferior to melphalan and dexamethasone (MDex).[89] On an intention-to-treat (ITT) basis, the median survival for MDex was 57 months vs 22 months for the ASCT arm. However, of the 50 patients randomized to receive ASCT, only 37 actually received the planned transplant and 9 of those died within 100 days, indicating an unacceptably high (24%) treatment-related mortality (TRM). In a 6-month landmark analysis, no difference in survival was noted between treatment arms, thus accounting for the survival disadvantage of ASCT to the very high TRM rate. In contrast, modern cohorts demonstrate a TRM of less than 5%,[6,79,90,91] suggesting inappropriate selection of patients in that study, which in turn limits its conclusions.

In contrast to that randomized study, numerous studies support the use of ASCT in selected patients, given high response rate, durability of response, and long-term survival effect. In the 4 largest modern series on ASCT in AL amyloidosis (with or without induction), HR was achieved in 83% to 94% of patients, hematologic CR in 43% to 56%, and OR in 56% to 69%, and median OS was 6.3 to 10.9 years.[6,91-93] The actuarial 15-year survival rate in our center among patients undergoing ASCT is 30%,[8] a figure that is expected to be higher with improvements in outcomes in recent years.[46] In a study focusing on AL patients surviving 10 years or more, those who underwent ASCT were less likely to require subsequent therapies compared with those receiving standard-intensity therapies.[7]

Guideline: Select candidates for ASCT on the basis of troponin level, systolic blood pressure, renal function, functional status, and physiologic age.

Level of Evidence: III

Grade of Recommendation: B

In early experience with ASCT, day 100 TRM was approximately 15% to 20%,[79,90,94] but with better careful selection, it has gradually declined to a single-digit percentage, reaching as low as 1% to 4% in high-volume centers.[79,91,94] Our eligibility criteria for ASCT are provided in Table 5. In our practice, we use a troponin T level of 0.06 ng/mL or more (or high-sensitivity troponin level $\geq$75 ng/L) as an exclusion factor, given a 28% 100-day all-cause mortality among these patients in contrast to a 7% all-cause mortality among those with a value below that threshold.[95,96] Another important contraindication to ASCT is low systolic blood pressure.[97,98] Patients with significantly impaired creatinine clearance are at risk for post-ASCT dialysis.[99,100] Collection of stem cells for storage can be considered in selected younger patients with high cardiac risk as they may become transplant eligible if organ function recovers with standard-intensity therapies.

Guideline: Dose-attenuated conditioning chemotherapy is not recommended for sicker patients.

Level of Evidence: III

Grade of Recommendation: C

In an effort to treat more patients with ASCT, dose-attenuated melphalan has been employed in patients with worse performance status, more organs involved, significant cardiac involvement, and older age. Consistently,

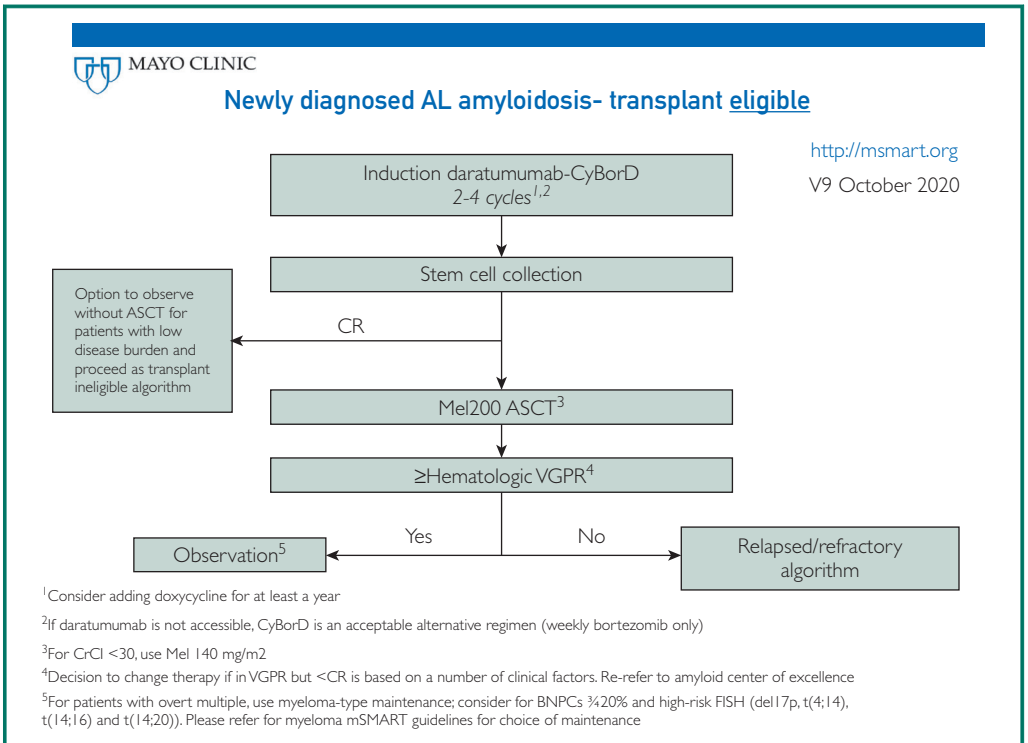

FIGURE 2. Treatment algorithm for transplant-eligible newly diagnosed AL amyloidosis patients. ASCT, autologous stem cell transplant; BMPCs, bone marrow plasma cells; CR, complete response; CrCl, creatinine clearance; CyBorD, cyclophosphamide, bortezomib, dexamethasone; FISH, fluorescence in situ hybridization; MEL200, melphalan 200 mg/m^2 conditioning; mSMART, Mayo Stratification of Myeloma and Risk-Adapted Therapy; VGPR, very good partial response.

this approach has resulted in lower HR rates including lower CR rates, inferior PFS and OS, and higher TRM rate.[6,93,101] Inferior survival and higher TRM in patients receiving an attenuated melphalan dose are not surprising because these patients are more frail. However, attenuated melphalan dose was an independent predictor for poor outcomes in the 2 largest studies of ASCT in AL amyloidosis from BU and Mayo Clinic.[6,93] In contrast, the UK group reported that an attenuated melphalan dose did not affect HR, OR, and OS, although in a quarter of the patients, the melphalan dose was unknown.[91]

Long-term survival appears to be unsurpassed if ASCT is performed in select patients at high-volume transplant centers with a low TRM, especially if CR is achieved.[6-8,102] In contrast, for those patients who have significant comorbidities meriting consideration of reduction of the conditioning melphalan dose (with the exception of reduced dose melphalan for patients with eGFR <30 mL/min per 1.73 m^2), transplant is likely not the preferred initial option.[6,89,93,95]

Guideline: Induction therapy before ASCT is recommended in all transplant-eligible patients.

TABLE 5. Mayo Eligibility Criteria for Autologous Stem Cell Transplant

"Physiologic" age ≤70 years
Performance score ≤2
Systolic blood pressure ≥90 mm Hg[a]
Troponin T level <0.06 ng/mL (or high-sensitivity troponin T level <75 ng/mL)
Creatinine clearance ≥30 mL/min[b] (unless on long-term dialysis)
New York Heart Association class I/II

[a]Caution as well for patients with systolic blood pressure <100 mm Hg.
[b]Selected patients may become eligible for autologous stem cell transplant with cardiac and renal transplant.

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Level of Evidence: III

Grade of Recommendation: C

Our recommendation for induction therapy in transplant-eligible patients is now broadened to include all patients, regardless of the degree of bone marrow plasmacytosis, given improvement in standard-intensity therapies and emerging data on the favorable benefit-risk balance of induction therapy. Moreover, several months are typically required to get a patient to transplant,[103] and it would be appropriate to reduce the load of the amyloidogenic light chains in the meantime to prevent further organ damage.

A small single-center randomized trial comparing 2 cycles of bortezomib-dexamethasone induction followed by ASCT (n=28) vs ASCT alone (n=28) has reported improved 1-year HR and CR rates favoring the induction arm (86% and 68% vs 54% and 36%, respectively).[104] Moreover, the respective 2-year OS rates were 95% and 69%, and the respective 2-year PFS rates were 81% and 51%. A phase 2 study with 50 transplant-eligible patients assessed the impact of 4 cycles of bortezomib-dexamethasone induction before ASCT.[105] The study failed to meet its primary end point because of a high dropout (30%), mainly as a result of treatment-related toxicity, which can be explained by enrollment in inexperienced centers for management of AL amyloidosis and the use of twice-weekly bortezomib.

A retrospective study by our group explored the role of induction therapy among 415 patients who underwent ASCT between 1996 and 2011.[106] Induction therapy was given to 35% of the cohort, half of which was in the form of corticosteroids only. Induction therapy did not affect post-ASCT HR or CR rate in those with 10% or less plasmacytosis. However, among those with more than 10% plasmacytosis, induction therapy significantly improved the post-ASCT response rate, with CR nearly doubled from 18% to 34%. In multivariate analysis, having no induction therapy was associated with a shorter survival, irrespective of the plasma cell burden.

Other reports on the benefit of induction therapy exist,[103,107] although they are limited by selection bias and low-level strength of evidence. Another study from the Pavia group reported the clinical outcomes of bortezomib induction followed by ASCT among 40% of patients who did not achieve a satisfactory response to cyclophosphamide, bortezomib, and dexamethasone (CyBorD) and were deemed transplant eligible.[108]

In the era of effective therapies, we recommend that induction therapy should be offered to all patients to increase the likelihood of a deep response after ASCT. Daratumumab-CyBorD is our recommended pre-ASCT induction, given its high efficacy and acceptable toxicity, as found in the ANDROMEDA study (discussed in detail in the non—transplant therapy section later). Alternatively, CyBorD can be offered as induction when daratumumab is not available. We recommend against twice-weekly bortezomib, which has a higher adverse effect profile, as therapy-related toxicity or organ deterioration while the patient is receiving induction therapy may adversely affect eligibility for ASCT.[105] Induction therapy may render transplant-ineligible patients eligible for transplant with improvement in organ function.[109]

The role of ASCT in patients who achieved CR to induction therapy remains unanswered. At this time, we recommend stem cell collection, whereas a decision on whether to pursue early ASCT should be made on an individual basis. Patients who may see greater benefit of early ASCT in this scenario are those with high-risk FISH abnormalities or concomitant active myeloma, but a definitive answer is lacking.

Guideline: Patients who did not achieve at least VGPR after ASCT should be offered an alternative therapy.

Level of Evidence: III

Grade of Recommendation: B

The concept of consolidation after ASCT has been assessed in several studies. Although it is a semantic distinction, achievement of less than VGPR after ASCT should be regarded as treatment failure and alternative therapy should be offered. However, the literature refers to therapy after ASCT with no

disease progression as consolidation, usually in the context of aiming at deeper response.

Sanchorawala et al[110] performed a prospective trial testing whether a second (tandem) ASCT could induce CR in patients who had not achieved CR after the first ASCT. There were 62 patients enrolled, and 27 patients achieved CR to first transplant. Of the 22 who did not achieve CR and could be considered for a second ASCT, 17 patients proceeded with this therapy and 5 more patients achieved CR. Although tandem ASCT may improve depth of response, its toxicity and the presence of alternative therapies make the tandem transplant model rarely used.

Two phase 2 trials tested the impact of consolidation. In these trials, patients not achieving CR received consolidative thalidomide with or without dexamethasone[111,112] or bortezomib and dexamethasone. In the study of thalidomide with or without dexamethasone, 31 patients began consolidation, but only 52% completed 9 months of treatment; 42% achieved a deeper HR. By ITT (which includes patients who died before response assessment was made), the HR and CR rates were 71% and 36%.[111] In the other study, 6 cycles of bortezomib and dexamethasone were given to 23 patients. Of these, 18 patients had improvement in their response depth, including 12 patients (52%) who achieved a CR.[112]

We published our experience with consolidation after ASCT in 72 patients, representing 15% of patients who underwent ASCT in our center between 2005 and 2017.[113] Consolidation was almost evenly divided between proteasome inhibitor (PI), immunomodulatory drug (IMiD), and PI-IMiD combination. Patients who received consolidation had a lower day +100 post-ASCT CR or VGPR than those who did not (35% vs 84%). With consolidation, the rate of CR or VGPR improved to 58%, mainly because of improvement in CR rate.

Guideline: Maintenance therapy after ASCT should be considered for patients with myeloma phenotype or high-risk FISH abnormalities.

Level of Evidence: V

Grade of Recommendation: D

Because there are no trials or series addressing this question, a recommendation on post-ASCT maintenance therapy is driven by expert opinion only. The goal of maintenance therapy is to provide continuation of response with low-intensity therapy. In MM, maintenance therapy with lenalidomide or bortezomib has been able to improve disease control, and for lenalidomide, survival benefit has been found in several studies as well as in a meta-analysis.[114] Most patients with AL do not have concomitant symptomatic myeloma; however, for those patients with concomitant myeloma (as defined by SLiM-CRAB criteria), maintenance therapy after ASCT should also take into consideration the myeloma part of the disease. Lenalidomide could be considered in those with concern for early relapse, assuming adequate cardiac reserve. In addition, patients with high-risk FISH abnormalities [del17p, t(4;14), t(14;16), t(14;20), gain 1q] tend to relapse early,[70,115,116] and maintenance therapy, preferably with PI, should also be considered in such patients. In our cohort of an ASCT population, maintenance therapy is given to approximately 5% of patients.

Guideline: For patients on hemodialysis, ASCT is feasible, especially if renal allograft is being considered.

Level of Evidence: IV

Grade of Recommendation: B

Once an AL patient has started dialysis, it is unlikely that renal function will recover without a renal allograft. Two studies have reported that ASCT can be safely performed in these patients with comparable outcome to those without end-stage renal disease (ESRD). The first study from BU reported on outcomes of 15 patients with ESRD undergoing ASCT for AL amyloidosis between 1994 and 2000.[117] The CR rate was 53%, and TRM was seen in 2 patients (13%). The OS was not different between the ESRD group and the non-ESRD group, but median survival was only 25 months, reflecting the early experience with ASCT. The second study from our group assessed the impact of timing of dialysis in AL

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TABLE 6. Bortezomib Combinations in Newly Diagnosed AL Amyloidosis[a]

Reference, year	No.	≥2 organs	Mayo 2004 stage (1/2/3a/3b)	HR/CR (%), ITT[b]	OR (%), ITT[b]	Median follow-up (mo)	Median survival
Manwani et al,[75] 2019	915	Median 2 organs	16/33/37/14	65/25 (n=819)	12-month: Heart 32.5 Kidney 15.4 Liver 30	23; 32 for living patients	6 years
Palladini et al,[53] 2015	230	Not provided	18/33/29/20	60/23	Heart 17 Kidney 25 Liver 32	25 for living patients	3-year 55%
Muchtar et al,[46] 2017	222	28%	7/35/34/24	60/21[c]	Heart 19[c] Kidney 25 Liver 14	33 for living patients[c]	21 months[c]
Venner et al,[192] 2014	69	Median 2.5	12/30/32/26	71/40.5	Not reported as ITT	12.7	1-year 65.2%
Shen et al,[193] 2019	62	Median 2	3b 45%	52/37	Heart 35	24	30 months
Jaccard et al,[125] 2014	60	Median 2	All stage 3	68/15	Heart 32	11.8	Not reached
Diaz-Pallares et al,[194] 2020	34	Not provided	Not provided	91/26.5	6-month: Heart 19 Kidney 32	24; 40 for living patients	Not reached

[a]CR, complete response; HR, hematologic response; ITT, intention to treat; OR, organ response.
[b]Data were modified from original data, if needed, to reflect intention-to-treat analysis (patients who died before response assessment are considered nonresponders).
[c]Data not reported in the original publication and generated from the original study data set for the manuscript.

patients undergoing ASCT. The 8 patients who had been on dialysis for more than 30 days before ASCT had similar outcome to those who never required dialysis.[100] These patients had the highest level of cardiac biomarkers, reflecting the impaired glomerular filtration rather than the cardiac status. Therefore, ASCT can be performed safely in hemodialysis patients, as long as there is attention to dose adjustment of melphalan and supportive care medications. Assessment of cardiac status to determine ASCT eligibility should follow other heart functional means rather than cardiac biomarkers.

Guideline: ASCT in patients with underlying lymphoproliferative disease or IgM monoclonal protein should be considered for eligible patients.

Level of Evidence: III

Grade of Recommendation: B

Limited information exists to guide treatment. The largest transplant series is from Mayo Clinic, in which 38 patients with an IgM monoclonal protein underwent ASCT.[118] Most patients were conditioned with melphalan alone (84%), whereas 16% of patients received BCNU-etoposide-cytarabine-melphalan (BEAM) conditioning. The HR rate was 92%, and the CR rate was 18%. Renal response was seen in 65% of patients and cardiac response in 60%. The median PFS and OS were 4 years and 9 years, respectively.

Initial Therapy for Patients Ineligible for Stem Cell Transplant

Guideline: Daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone is the new standard of care for transplant-ineligible newly diagnosed AL amyloidosis patients.

Level of Evidence: I

Grade of Recommendation: A

At the time of writing of the consensus statement, the initial results from the ANDROMEDA study were presented. This is

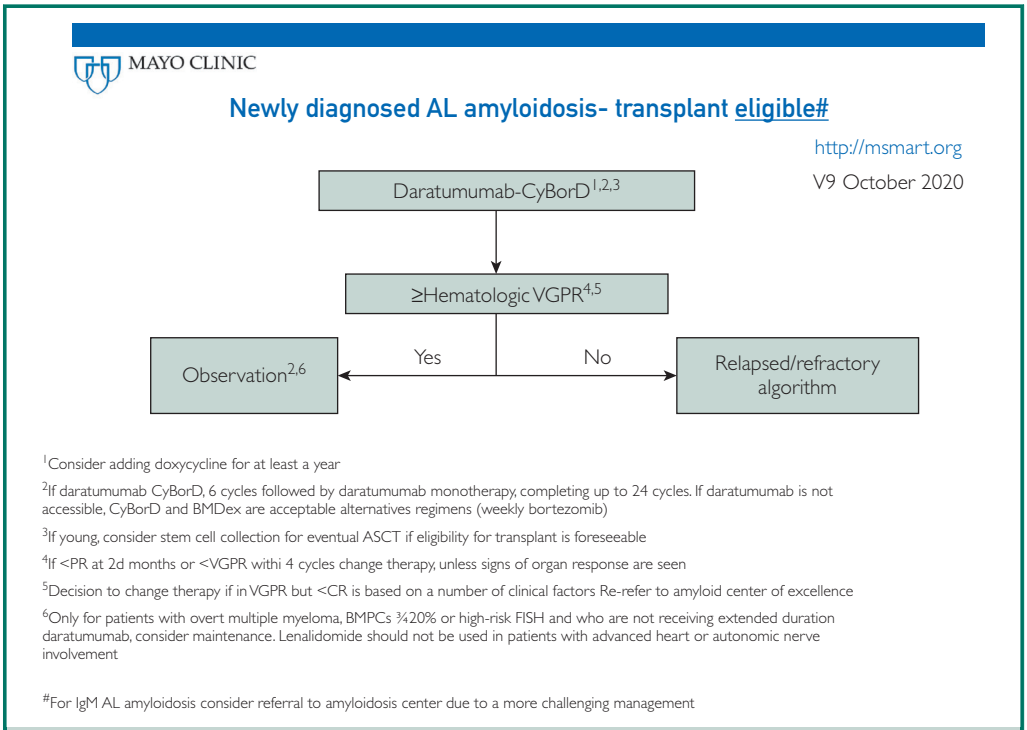

FIGURE 3. Treatment algorithm for transplant-ineligible newly diagnosed AL amyloidosis patients. ASCT, autologous stem cell transplant; BMDex, bortezomib, melphalan, dexamethasone; BMPCs, bone marrow plasma cells; CR, complete response; CyBorD, cyclophosphamide, bortezomib, dexamethasone; FISH, fluorescence in situ hybridization; PR, partial response; VGPR, very good partial response.

the largest randomized controlled trial to date in AL amyloidosis with 388 patients. Newly diagnosed AL patients were randomly assigned to daratumumab (anti-CD38 monoclonal antibody) in combination with CyBorD (investigational arm, n=195) or CyBorD (control arm, n=193). CyBorD was given for 6 cycles in each arm and daratumumab in standard schedule and dosing up to a total of 24 cycles. Patients with Mayo stage 3b were excluded. The median duration of treatment was 9.6 months for daratumumab-CyBorD and 5.3 months for CyBorD. The HR and CR rates were significantly higher in the investigational arm compared with the control arm (HR, 92% vs 77%; CR, 53% vs 18%). However, the investigators used a modified CR definition in that study, which included negative serum or urine immunofixation and involved light chain below the upper limit of normal, irrespective of normalization of serum FLC ratio. The 6-month cardiac and renal response rates favored the treatment arm (cardiac response, 42% vs 22%; renal response, 54% vs 27%). The toxicity profile was similar between arms, but the rate of pneumonia was 8% in the daratumumab-CyBorD arm compared with 4% in the CyBorD arm. The main design caveat of this study is the longer treatment duration in the daratumumab-CyBorD arm compared with the control arm, which affects the interpretation of some of the study end points.

Given these results, daratumumab in combination with CyBorD was recently approved by the Food and Drug Administration, making this combination the preferred initial therapy for AL amyloidosis.

Guideline: In the absence of access to frontline daratumumab, an acceptable first-line therapy for transplant-ineligible patients is CyBorD or bortezomib, melphalan, and dexamethasone (BMDex).

Level of Evidence: II for BMDex; III for CyBorD

Grade of Recommendation: A

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Bortezomib success in AL amyloidosis probably stems from a higher sensitivity of AL plasma cells to proteasome inhibition owing to toxic light chain–induced cellular stress.[119]

In a randomized study comparing BMDex (n=53) with MDex (n=56), the BMDex arm achieved higher HR rate (79% vs 52%), higher VGPR/CR rate (64% vs 39%), and longer PFS or OS compared with the MDex arm, providing high-level evidence of proof for the importance of bortezomib as initial therapy for AL amyloidosis.[120] However, the bulk of the experience with bortezomib in the upfront setting comes from retrospective studies. A summary of the major studies assessing bortezomib in combination with alkylator and dexamethasone in the upfront setting is listed in Table 6. The HR rate is 60% to 80%, with CR in the 20% to 25% range. The largest study on first-line bortezomib comes from the UK group, in which 915 patients were mostly treated with CyBorD between 2010 and 2017.[75] Response data were available for 819 patients. On ITT analysis, the HR and CR rates were 65% and 25%, respectively. The median OS was 6 years. A third of the study population died without progression to second-line therapy, and of the remaining patients, 55% did not require second-line therapy at the 7-year landmark.

In resource-limited areas, CyBorD (or other bortezomib-containing regimens) should continue to be the standard of care for newly diagnosed AL amyloidosis patients (Figure 3). The choice between CyBorD and BMDex (or other bortezomib-containing regimens) is not fully guided as there is no comparison between the various regimens. In the United States, CyBorD is the standard, given its early introduction[121] and possible better tolerance compared with BMDex. However, because response to MDex is not affected by t(11;14),[70] it may be reasonable to consider BMDex in the face of t(11;14). In contrast, if there is a plan for stem cell harvest and possible future ASCT, melphalan should be avoided or limited as it can deleteriously affect the ability to mobilize stem cells.[122]

Guideline: Bortezomib should be administered subcutaneously once weekly at an initial dose of 1.3 to 1.6 mg/m^2. Lower initial dose (0.7-1.0 mg/m^2) can be considered in those with advanced cardiac disease.

Level of Evidence: III

Grade of Recommendation: B

In a phase 1/2 study using single-agent bortezomib in the relapsed setting, once-weekly bortezomib at a dose of 1.6 mg/m^2 was associated with a lower toxicity profile compared with twice-weekly bortezomib at a dose of 1.3 mg/m^2, including fewer cardiac events and orthostatic hypotension and less dose modification.[123] The twice-weekly bortezomib was possibly linked to death in 2 of 34 patients but none in the 18 patients treated with once-weekly bortezomib. Moreover, the CR rate was higher in the once-weekly bortezomib group. Lower bortezomib doses (0.7-1.0 mg/m^2) led to fewer adverse events but also lower response rate.

The Greek group reported outcomes for dose-adjusted bortezomib-dexamethasone (bortezomib 1.3 mg/m^2 and dexamethasone 20 mg weekly) for patients with advanced cardiac stage, age older than 70 years, low performance status, low systolic blood pressure (<100 mm Hg), or preexisting neuropathy.[124] These patients had similar HR, CR, and OR rates compared with those who received full-dose bortezomib-dexamethasone (bortezomib 1.3 mg/m^2 and dexamethasone 40 mg on days 1, 4, 8, and 11 every 21 days). The 3-month death rate was significantly lower in the dose-adjusted group compared with the full-dose group (4.5% vs 36%), despite worse baseline characteristics. In an unselected AL population not eligible for ASCT, we reported that bortezomib was associated with increased risk of early death compared with MDex after accounting for the number of involved organs, dFLC, and Mayo stage.[46] However, this observation should be taken cautiously, given the retrospective nature of the study, leading to potential selection bias and lack of data on treatment intensity in many patients treated in outside facilities.

Our overall recommendation is to administer bortezomib once weekly rather than twice

weekly, with close monitoring for toxic effects including cardiac toxicity, hypotension, and neuropathy. In patients with advanced heart disease (Mayo stage 3b or New York Heart Association class III/IV), an initial lower dose of bortezomib can be considered and increased if tolerated. The dexamethasone weekly dose should be adjusted to organ involvement and performance status to avoid excess toxicity. This is particularly important in patients with advanced heart disease or nephrotic syndrome, in which dexamethasone can aggravate fluid retention.

Guideline: Duration of induction is at least 6 cycles in patients with no coexisting MM or high-risk FISH abnormalities.

Level of Evidence: III

Grade of Recommendation: B

There are no randomized trials that address the optimal duration of therapy. However, given the typical low clonal burden, therapy is generally administered for a limited period. The median number of cycles in clinical practice is 5,[46,75,125] which is the basis for our recommendation for at least 6 cycles of therapy in most patients (Figure 3). However, patients who achieved a rapid response with a plateau in response (including involved FLC level) may be offered fewer than 6 induction cycles.

Guideline: Patients with concomitant symptomatic MM or with high-risk FISH abnormalities should receive induction for 6 to 12 months with consideration of maintenance therapy.

Level of Evidence: IV

Grade of Recommendation: C

There is considerable lack of data on the management of AL amyloidosis patients with concomitant symptomatic myeloma (SLiM-CRAB features) or high-risk FISH abnormalities. These 2 subgroups compose approximately 10% of AL amyloidosis patients each and overlap each other.[66] As discussed before, whereas the short-term survival is dictated by the organ pattern and the degree of heart involvement, the plasma cell clone features, such as the attainment of hematologic CR, are important for long-term survival.[6-8] High-risk FISH abnormalities predict worse outcomes in myeloma patients, but their role in the AL population is not fully defined, given their rarity. In a multicenter study of 44 AL patients with del17p, the 2 independent predictors for survival were cardiac stage and response to therapy.[72] Patients with del17p in more than 50% of the plasma cells had a trend toward inferior survival.

With the reservation of data paucity, management of AL amyloidosis patients with concomitant symptomatic myeloma or high-risk FISH abnormalities should consider employment of myeloma treatment schemes in terms of duration of therapy and the use of maintenance therapy. We recommend 6 to 12 cycles of therapy in these patients to align with the general recommendation on induction therapy in transplant-ineligible myeloma patients. Because transplant-ineligible AL amyloidosis patients are often frail, one needs to balance the putative risk of myeloma "high-risk features" with the known toxic effects of therapy in AL patients. Because IMiDs are typically poorly tolerated in patients with significant cardiac involvement, if maintenance is considered in these patients, bortezomib or ixazomib maintenance may be preferred.

Initial Therapy in Certain Subpopulations of Interest

Guideline: Patients with t(11;14) have an inferior HR and survival after bortezomib-based therapy, and alternative therapies should be considered early if HR is suboptimal.
Level of Evidence: III

Grade of Recommendation: B

Translocation t(11;14) is present in approximately 50% of AL amyloidosis patients.[70] Several studies have reported that patients harboring this aberration and who were treated with bortezomib have lower

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response rate and inferior PFS and OS compared with non-t(11;14) patients treated with bortezomib.[68-70] However, the overall management of these patients should follow the treatment guidelines of the general AL amyloidosis population, with change in therapy if adequate response is not achieved.

Guideline: In patients with neuropathy, bortezomib should be avoided.

Level of Evidence: I

Grade of Recommendation: A

Bortezomib can severely aggravate autonomic or peripheral neuropathy, and its use should be discouraged in those with grade 2 or worse neuropathy (≥severe paresthesias or mild weakness interfering with daily function). Options in this population of patients include MDex,[126] carfilzomib (in nonadvanced cardiac patients),[127] and daratumumab.[128]

Guideline: In patients on hemodialysis, attention is required for dose modifications.

Level of Evidence: III

Grade of Recommendation: C

Patients on long-term dialysis require adjustment of therapy for their renal impairment. Daratumumab has no renal clearance and is not dialyzable, and thus no dose adjustment to renal function is needed. It can be given after dialysis unless the patient is volume overloaded. In that case, it should be given before dialysis so the volume can be removed. Subcutaneous daratumumab may overcome the fluid overload that can be seen with intravenous administration of daratumumab.

Cyclophosphamide should be capped at 300 mg per dose. It should be given after dialysis because it can be removed with dialysis. Whereas bortezomib and dexamethasone do not require renal dose adjustments, melphalan dose should be reduced 30% to 50%, depending on the severity of the renal dysfunction. Attention should also be given to dose adjustment of supportive care medications, such as acyclovir and sulfamethoxazole/trimethoprim, both of which should be given after dialysis.

Guideline: Non-ASCT therapies for AL patients with underlying lymphoproliferative disease or IgM monoclonal gammopathy yield lower responses, and guidance on optimal therapy is lacking.

Level of Evidence: IV

Grade of Recommendation: C

IgM-associated AL amyloidosis is a rare clinical entity with distinctive clinical characteristics.[129] Some cases may be "localized forms," in which there is only nodal or soft tissue involvement without visceral involvement. These cases can merely be observed, with no indication for systemic therapy. Chemotherapy is more often reserved for those cases in which there is typical amyloid deposition in viscera. Historically, regimens have been borrowed from both the myeloma and the Waldenström macroglobulinemia armamentarium but were not tested systematically. These treatments include cladribine, fludarabine, rituximab, chlorambucil, cyclophosphamide, vincristine, doxorubicin, melphalan, corticosteroids, PIs, IMiDs, and ASCT.[129-133] However, IgM amyloidosis is characterized by lower response rate and poorer survival when adjusted to Mayo cardiac stage compared with non-IgM AL amyloidosis.[129] The response rate in the major studies was 32% to 82%, with a CR rate at 0% to 20%.[129-133] Response was higher with use of bortezomib, rituximab-based chemoimmunotherapy, and IMiDs compared with a single-agent alkylator.[130-132]

In a study of 75 patients with IgM amyloidosis, 3 distinct morphologic-genomic subtypes were found: lymphoplasmacytic (63%), pure plasma cell neoplasm (23%), and other (14%).[129] Compared with the pure plasma cell neoplasm type, patients with the lymphoplasmacytic type had a higher degree of marrow involvement and a higher degree of cardiac involvement, and all were positive for the $MYD88^{L265P}$ and CXCR4 mutations. Patients with pure plasma cell neoplasm were exclusively positive for t(11;14). Survival was

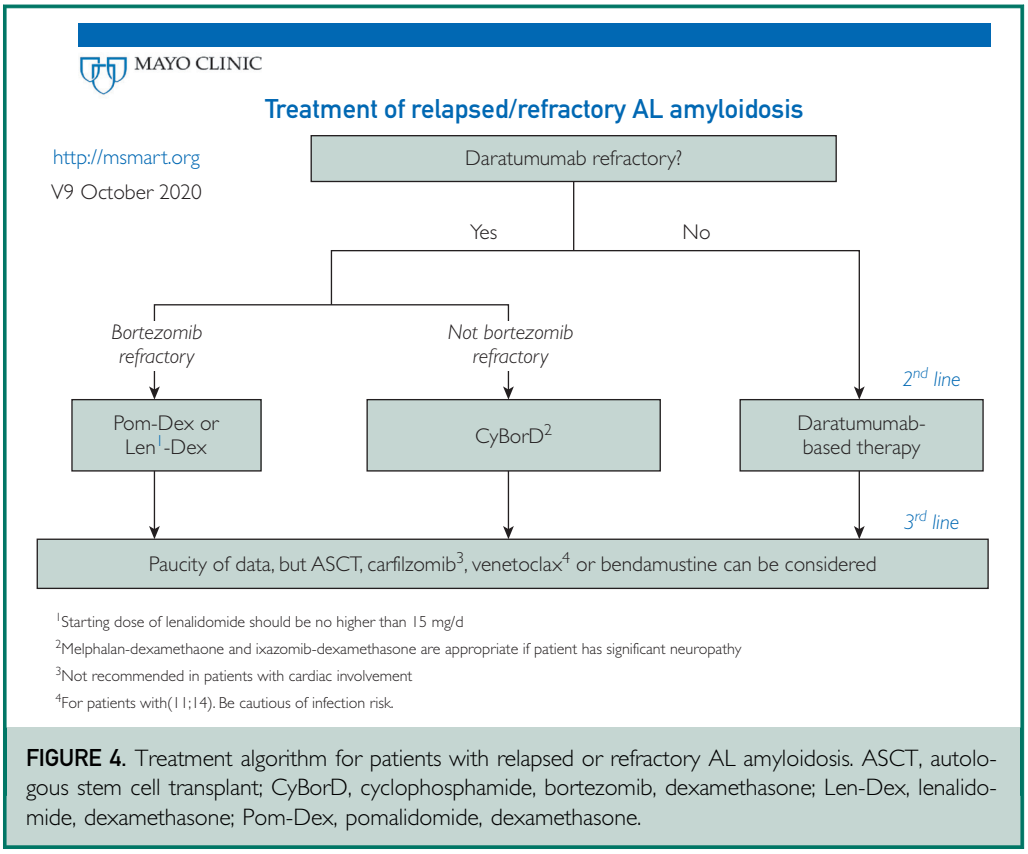

FIGURE 4. Treatment algorithm for patients with relapsed or refractory AL amyloidosis. ASCT, autologous stem cell transplant; CyBorD, cyclophosphamide, bortezomib, dexamethasone; Len-Dex, lenalidomide, dexamethasone; Pom-Dex, pomalidomide, dexamethasone.

not different between lymphoplasmacytic and pure plasma cell neoplasm types, but comparison is limited by small numbers. This study hypothesized that the lower HR in IgM amyloidosis compared with non-IgM amyloidosis is tied to these different subtypes and that if therapy will be guided by the underlying clone, response rate should improve.

We encourage referral of patients with IgM amyloidosis to an amyloidosis center to optimize diagnosis and management in an effort to improve survival in this rare subset of patients.

Treating Relapsed or Refractory AL Amyloidosis

Guideline: For patients not achieving hematologic VGPR (and for some not achieving hematologic CR), one should move down the relapsed/refractory management algorithm.

Level of Evidence: II

Grade of Recommendation: A

As discussed in the first-line therapy section, the ideal is to achieve hematologic CR because clone persistence can cause organ progression or less substantial organ improvement. The importance of balancing the desire to obtain the deepest responses and therapy-related toxicity cannot be overemphasized.

Guideline: Salvage therapy for patients previously achieving VGPR or better should be considered in the face of rising dFLC before the development of organ progression, even if hematologic progression is not met.

Level of Evidence: III

Grade of Recommendation: C

The decision on when to change therapy in the face of inadequate response or to reinstitute therapy for relapsed disease is a matter of ongoing debate.[134,135] We assessed the timing of initiation of second-line therapy among 235 patients who initially were treated

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TABLE 7. Daratumumab in Relapsed/Refractory AL Amyloidosis[a]

	No.	Design	Median time from diagnosis	Prior lines, median	No. of cycles, median	Median time to best response	HR/CR (%), ITT[b]	OR (%), ITT[b]	Median follow-up (mo)	Median survival
Kimmich et al,[141] 2020 (DD portion)	106	Retrospective	29 months	2	5 (14 infusions)	Not provided	64/8	Cardiac 6 months: 22 Renal 6 months: 24	21.2	25.6 months
Kimmich et al,[141] 2020 (DVD portion)	62	Retrospective	5 months	1	5 (14 infusions)	Not provided	66/11	Cardiac 6 months: 26 Renal 6 months: 24	16.7	Not reached
Chung et al,[195] 2020	72	Retrospective	21 months	2	Not provided	Not provided	77/40 (72% evaluable)	Cardiac 55 (54% evaluable) Renal 52 (53% evaluable)	27	Not reached; 2-year 86.7%
Abeykoon et al,[196] 2019	44	Retrospective	4 years	3	8	5.7 months	83/80/17	Cardiac 61 Renal 50 Liver 7	10.2	Not reached
Roussel et al,[140] 2020	40	Prospective	23 months	3	6	Not provided	55/7.5	Renal 31 Cardiac 25	26.4	Not reached; 2-year 74%
Sanchorawala et al,[139] 2020	22	Prospective	48 months	2	10	3 months	90/41	Renal 67 Cardiac 50	20 for survivors	28 months
Van de Wyngaert et al,[197] 2020	15	Retrospective	21 months	2	12	3 months	80/40	Renal 33 Cardiac 33	7.9	Not provided
Schwotzer et al,[198] 2019	10	Retrospective	11.9 months	3	80% 9 cycles	2 months	90/20	Cardiac 50 Renal 0	10	Not provided

[a]CR, complete response; DD, daratumumab-dexamethasone; DVD, daratumumab-bortezomib-dexamethasone; HR, hematologic response; ITT, intention to treat; OR, organ response.
[b]Data were modified from original data, if needed, to reflect intention-to-treat analysis (patients who died before response assessment are considered nonresponders).

BOX. Levels of Evidence and Grades for Recommendations

Level of Evidence	
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies Randomized trials with low false-positive and low false-negative errors (high power)
II	Evidence obtained from at least one well-designed experimental study Randomized trials with high false-positive or 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 for Recommendation	
A	There is evidence of type I or consistent findings from multiple studies of types II, III, or IV.
B	There is evidence of types II, III, or IV and findings are generally consistent.
C	There is evidence of types II, III, or IV but findings are inconsistent.
D	There is little or no systematic empirical evidence.

with ASCT.[136] The median time between ASCT and second-line therapy was 2 years. At the time of second-line therapy, the median dFLC was 100 mg/L, being 42% of the dFLC at the time of diagnosis. The dFLC at second-line therapy was lower in the 2009-2016 period compared with the 1997-2008 period (70 mg/L vs 120 mg/L), probably representing the increase in availability of effective therapies in recent years as well as a lower dFLC threshold to restart therapy. Organ progression was noted in 63% of the patients. On multivariate analysis, dFLC of 50 mg/L or more and organ progression at second-line therapy were adversely associated with survival. The importance of initiation of second-line therapy before organ progression was also reported by Palladini et al.[137] In this study, 92 patients required second-line therapy, at a median dFLC of 55 mg/L. Cardiac and renal progression was noted in 22% and 12% of patients. The only independent predictor for survival was cardiac progression. Unfortunately, organ function deterioration during second-line therapy is seen in half of the patients and, in addition to the risk of death, is also associated with an increase in medical cost.[138]

Guideline: Daratumumab-based therapy is the preferred salvage therapy in patients not refractory to daratumumab.

Level of Evidence: II

Grade of Recommendation: A

There are considerable data from prospective and retrospective studies to support daratumumab use as second-line therapy, given high efficacy and good tolerability (Figure 4). Table 7 summarizes the important clinical data on daratumumab in AL amyloidosis in the relapsed/refractory setting. Hematologic responses are seen in most patients, with the rate of VGPR or better at approximately 60% to 80% and CR in approximately 10% to 40% of patients. Responses are rapid, within 1 to 3 months of therapy, and are lasting. It is unlikely that response will improve beyond what has been achieved within the first 3 months of therapy.[139]

Daratumumab as monotherapy or in combination with dexamethasone (often given as premedication) is sufficient in most patients. Overall, combination with other agents (such as bortezomib or IMiD) is usually not necessary as data do not suggest that it leads to clear improvement in response depth. Duration of therapy is not well defined.

Several predictors for response and survival among daratumumab-treated patients were reported. In 1 study, the dFLC after 1 infusion (either as absolute number or

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as percentage reduction) was the only parameter to predict response.[140] In a larger study of 106 patients, a dFLC greater than 180 mg/L at therapy initiation was an independent poor predictor for VGPR or better response. The presence of dFLC greater than 180 mg/L, high urine albumin to creatinine ratio (>220 mg/mmol), and cardiac stage 3b were independent predictors for poor PFS.[141] The finding of high albumin to creatinine ratio to predict inferior PFS was explained by loss of daratumumab in the urine in patients with nephrotic-range proteinuria. Indeed, the authors described 7 patients with suspected or confirmed daratumumab in the urine, suggesting that heavy proteinuria causes lower availability of daratumumab, affecting its efficacy.

Daratumumab was well tolerated in all assessed trials. In the 2 prospective studies, the rate of infusion-related reactions was 23% and 52%, mostly as grade 1 or grade 2. Other adverse effects include infections, fatigue, cardiac arrhythmia, congestive heart failure, lymphopenia, diarrhea, anemia, and thrombocytopenia. Daratumumab is associated with the development of hypogammaglobulinemia (which may be present at treatment onset and further exacerbated by therapy). The use of intravenous immunoglobulin may be justified in those who experienced serious infections after therapy and in whom serum IgG is below 500 to 600 mg/dL, but this practice was not assessed for efficacy.

Guideline: Bortezomib-based regimen or ixazomib-based regimen is the preferred salvage therapy in daratumumab-refractory and bortezomib-sensitive patients.
Level of Evidence: III

Grade of Recommendation: B

Proteasome inhibitor–based therapy remains the preferred salvage therapy after daratumumab failure, given better results for a PI-based therapy in relapse/refractory AL amyloidosis and better tolerability compared with IMiD-based therapy (Figure 4).

Data on bortezomib in relapse/refractory amyloidosis were extensively reviewed in our prior mSMART consensus statement for AL amyloidosis.[10] In studies with exclusively or predominantly relapse/refractory patients, the HR was 70% to 80%, and the CR rate was 15% to 40%.[123,142,143]

Ixazomib was also assessed in relapse/refractory AL amyloidosis. In a phase 1/2 study, 27 patients were treated with ixazomib.[144] The maximum tolerated dose was 4 mg. Patients were heavily pretreated, and 70% had previously received bortezomib. The HR was 52%, and CR was 10%. Responses were higher in PI-naïve patients. In the Tourmaline-AL1 phase 3 study, 168 PI-sensitive patients with relapse/refractory disease were randomized between ixazomib-dexamethasone and 1 of 5 physician's choice salvage regimens (mostly chosen were MDex and lenalidomide-dexamethasone).[145] The study did not meet its primary end point of superior HR in the ixazomib-dexamethasone group (ixazomib-dexamethasone, 53%; physician's choice, 51%). However, patients treated with ixazomib-dexamethasone had better CR rate (26% vs 18%) and OR (36% vs 11%), longer time to treatment failure (10 vs 5 months), and longer PFS (11 vs 7 months) but no OS advantage. This study, despite its limitations, brings ixazomib-dexamethasone as a plausible treatment option for PI-sensitive relapse/refractory AL amyloidosis. Given the low incidence of neuropathy, ixazomib-dexamethasone (as well as MDex) can be used in these patients instead of bortezomib to reduce further neurologic decline.

Guideline: Among daratumumab- and bortezomib-refractory patients, lenalidomide or pomalidomide in combination with dexamethasone is the preferred salvage therapy.

Level of Evidence: III

Grade of Recommendation: B

The use of IMiD in AL amyloidosis is challenging because of poor tolerability at standard dosing. Thalidomide is not recommended in the treatment of AL amyloidosis because of high toxicity. Lenalidomide is also not well tolerated in AL

amyloidosis and generally should be restricted to use in the relapsed/refractory setting. Studies with lenalidomide in combination with dexamethasone included newly diagnosed as well as relapse/refractory patients, which may affect interpretation of the results.[146-148] On ITT, HR was 38% to 47%, and CR was 0% to 21%. The ORs were infrequent, as high as 21%.[146] A lenalidomide dose greater than 15 mg/d was not tolerated, and the dose was often reduced to 5 to 10 mg/d. The most common toxic effects encountered in these trials include fatigue, neutropenia, thrombocytopenia, rash, infections, and venous thromboembolism. An increase in NT-proBNP and worsening renal function were also frequently seen and required close monitoring, treatment interruptions, and dose adjustments. Lenalidomide in combination with an alkylator and dexamethasone yielded slightly better HR of 40% to 60%, with CR of approximately 10% and infrequent ORs in most studies.[149-154]

A pomalidomide and dexamethasone combination was assessed in a total 87 relapse/refractory AL amyloidosis patients in 3 prospective studies, finding HR of 44% to 61%, CR of 3% to 30%, and OR of 7% to 17%.[155-157] Cardiac response assessment was usually not feasible because of a paradoxical rise in NT-proBNP as seen with lenalidomide.

Guideline: Options for third-line salvage therapy in AL amyloidosis are limited.

Level of Evidence: IV

Grade of Recommendation: C

Options for salvage therapy in AL amyloidosis after the aforementioned treatments have been used are limited. Carfilzomib has been tested in a phase 1 study but was associated with significant cardiac toxicity and therefore is not recommended in cardiac patients.[158] Venetoclax, a BCL-2 inhibitor, was found in MM to be active mainly among those with t(11;14), a genetic aberration present in approximately half of AL patients. Data on its efficacy and safely in AL are limited. We reported on the outcomes of 12 AL patients treated with venetoclax either as a single agent or in combination.[159] Most patients had t(11;14). Of the 8 evaluable patients for response, 7 patients responded, all with a VGPR or CR. Therapy was well tolerated. The use of venetoclax in t(11;14) AL amyloidosis warrants further assessment, given data from MM and these results. Other options to consider include second ASCT in eligible patients,[160] elotuzumab in combination with an IMiD,[161] and bendamustine.[162]

THIRD PILLAR: SUPPORTIVE THERAPY FOR AL AMYLOIDOSIS

Providing supportive care for patients with AL amyloidosis is challenging and requires a multidisciplinary approach based on the predominant involved organs and symptoms. A palliative care team is invaluable in counseling patients with advanced illness on symptom management, in providing psychosocial and spiritual support for patients and families, and in assisting with establishment of goals of care and advance care planning. This aspect of care is pivotal and should be addressed at the same time as therapy.

Guideline: Diuretics are the mainstay of management of volume overload due to congestive heart failure, nephrotic syndrome, or therapy.

Level of Evidence: IV

Grade of Recommendation: D

Guideline: Beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers should be used with great caution in cardiac amyloidosis.

Level of Evidence: V

Grade of Recommendation: D

Patients with cardiac amyloidosis typically have severe diastolic dysfunction with a nondilated ventricle, leading to increased filling pressures. Although the ejection fraction is preserved in most patients, stroke volume is

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reduced and relatively fixed because of restrictive filling. Patients with advanced cardiac amyloidosis are often dependent on higher heart rates to maintain cardiac output. The use of standard medical therapy for heart failure with reduced ejection fraction, specifically beta blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, often worsens patients' clinical status. Beta blockade may cause profound hypotension and worsen 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. Diuretics are the mainstay of care, with the best results achieved with a combination of loop diuretics and mineralocorticoid receptor antagonists, such as spironolactone. Metolazone or periodic thoracentesis may be considered in select cases.[163]

Patients with cardiac amyloidosis are at risk for intracardiac thrombi[164,165]; in one study, 35% of patients with AL amyloidosis who had transesophageal echocardiography had atrial thrombus, even in the absence of atrial fibrillation. The majority of thrombi were located in the right or left atrial appendages.[165] Anticoagulation should be considered, recognizing that life-threatening bleeding is a potential risk. Despite adequate anticoagulation, intracardiac thrombus may persist. Transesophageal echocardiography to exclude intracardiac thrombus is recommended before elective cardioversion, even among those receiving adequate anticoagulation.[166]

For those patients with atrial fibrillation, rate control can be challenging because beta blockade and calcium channel blockers are often poorly tolerated. Digoxin may be safely used in low doses with frequent monitoring of electrolytes and kidney function, despite that it is traditionally considered to be contraindicated.[167] Nondihydropyridine calcium channel blockers should be avoided because of the associated bradycardia and negative inotropic effects.[168] 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.[169,170] The role of implantable cardioverter-defibrillators is controversial in these patients; both successes and failures have been documented,[170-173] and studies to date have not found a survival advantage.[174] 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.[175]

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

Level of Evidence: V

Grade of Recommendation: D

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

Level of Evidence: IV

Grade of Recommendation: D

Amyloidosis patients 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 and carpal tunnel braces are of benefit. The autonomic insufficiency can be difficult to manage, especially among patients with severe nephrotic syndrome or severe cardiomyopathy. Compression garments, such as compression stockings or abdominal binder, and regular exercise are helpful in treatment of orthostatic hypotension. Increased daily water and sodium intake and fludrocortisone are useful only in a minority of these patients because they may aggravate congestive heart failure

or peripheral edema. The α_1-adrenergic receptor agonist midodrine, the α- and β-adrenergic agonist droxidopa, or the anticholinergic pyridostigmine can improve neurogenic orthostatic hypotension,[176] 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

The rationale for using doxycycline in amyloidosis comes from in vitro studies and mouse models finding that doxycycline inhibits the formation of and disrupts amyloid fibrils.[177,178] Two retrospective studies have reported a survival advantage for doxycycline in patients with AL amyloidosis.[179,180] The first assessed the survival in patients following ASCT based on biologic randomization of the anti-infective prophylaxis in the first year after ASCT.[179] Of 455 evaluated patients, 77% received oral penicillin, which is the standard antibacterial prophylaxis after ASCT, whereas 23% received oral doxycycline because of a history of penicillin allergy. Among patients who achieved HR to ASCT, oral doxycycline was associated with a survival advantage. The second study was a case-control study involving cardiac AL amyloidosis patients who were treated with standard chemotherapy.[180] The 30 patients treated with doxycycline were matched to controls (n=73) who did not receive doxycycline. The HR rate was significantly higher in the doxycycline group compared with the control group (93% vs 59%), mainly owing to higher CR rate as well as higher rate of cardiac response. As a result, survival advantage was noted in the doxycycline group over the control group.

Organ Transplant

Solid organ transplant is a controversial intervention among patients with AL amyloidosis. Because the disease is systemic, life-threatening, and presumably incurable, there is concern that the amyloid will either recur in the transplanted organ or progress in another organ, resulting in a poor outcome. The poor outcomes of AL amyloidosis in general have also contributed to low enthusiasm for organ transplant, given the organ shortage and the need to select patients who have higher survival likelihood. The best outcomes have occurred in the setting of careful selection of patients, excluding patients with clinically evident multiorgan involvement, and among those who received effective chemotherapy to eradicate the clone either before or after the solid organ transplant.

Guideline: Heart transplant for AL amyloidosis can be considered in very select cases.

Level of Evidence: III

Grade of Recommendation: C

The use of orthotopic heart transplant for AL amyloidosis has declined over the years, given unfavorable results in this group of patients. In the largest series to date with 23 patients, the median OS was 3.5 years, with 1-year survival of 77%.[181] Progressive amyloidosis was the cause of death in 60% of those who died. The best outcomes were achieved in those who attained hematologic CR. In comparison, for nonamyloid patients who underwent orthotopic heart transplant in the same era, the survival rate at 5 years was lower by half.

With the availability of more effective therapies in the current era and as CR is more a reality, highly selected patients may gain benefit from a heart transplant. Patients with persistent heart failure with minimal or no extracardiac involvement who preferably have achieved hematologic CR are potential candidates for heart transplant. We do not recommend upfront heart transplant to increase ability to deliver intensive therapy (including ASCT) in younger patients, given the limited organ supply and plethora of therapies besides ASCT that can effectively induce a deep response.

Guideline: Kidney transplant is feasible in selected cases with ESRD.

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Level of Evidence: III

Grade of Recommendation: B

Outcome studies on kidney transplant in AL amyloidosis have been reported by several groups. The most prominent reports are those of the BU[182] and Mayo Clinic[183] groups. The BU study with 49 patients reported a good graft survival at 1, 3, and 5 years, reaching 94%, 89%, and 81%, respectively. Those who attained CR or VGPR to therapy had longer graft survival and OS compared with those who achieved PR or no response. The Mayo group study included 75 patients, and the 1-, 3-, and 10-year graft survival rates were 98.6%, 96.7%, and 88.5%, respectively. In this larger cohort, the deeper the HR, the better the survival of the graft and patients, with the best outcome seen in those who reached a CR, but it remained also acceptable for those with a VGPR response.

It is our current practice to offer renal allograft to AL patients with ESRD who have already achieved CR or VGPR.

Guideline: Liver transplant for AL amyloidosis is not recommended.

Level of Evidence: V

Grade of Recommendation: C

Unlike for hereditary amyloidosis, liver transplant is rarely performed for patients with AL amyloidosis. Outcomes are poor, as illustrated by 1-year and 5-year OS rates of 33% and 22% in a series of 9 patients receiving a transplant in the United Kingdom.[184]

Treating Localized Amyloidosis

Treatment of localized amyloidosis is guided by the patient's severity of symptoms. Most patients, in the Mayo cohort as well as in the UK cohort, required therapy.[40,41] Treatment in most cases is by surgical or endoscopic removal of the amyloid. Less frequently, radiotherapy has been used. Systemic therapy has been anecdotally reported and should be rarely used, if ever. Laser resection is reserved for critical areas where excision needs to be precise to minimize damage to vital structures. The usual treatment of tracheobronchial AL amyloidosis is yttrium-aluminum-garnet laser resection of the tissue and, more recently, external beam radiation therapy.[185] For urothelial localized amyloidosis, surgical resection[186] and dimethyl sulfoxide instillation[187] are the standard approaches. In the Mayo and UK group studies, the overall recurrence rate of localized amyloidosis was 17% and 21%, respectively. However, location-specific case series have reported recurrence rate in the 50% range for urothelial,[188] laryngeal,[189] and tracheobronchial amyloidosis.[190]

FUTURE DIRECTIONS

Since the previous mSMART guidelines for AL amyloidosis 6 years ago, there have been significant improvements in the diagnostic and therapeutic domains, requiring the current guideline update. These major developments have resulted in continuous improvement in outcomes for patients. However, the main barrier to outcome improvement remains early recognition. The importance of early recognition cannot be overemphasized, especially in the face of effective therapies, as the greatest benefit of therapy is seen in those with the least organ impairment.[84] Raising awareness for disease recognition should be broad, given the systemic nature of the disease, and it is best accomplished by using general medicine and subspecialties journals and meeting platforms. A multidisciplinary team dedicated to the care of amyloidosis patients will further enhance the broad dissemination of awareness and knowledge on the management of these patients.

With improvement in outcomes, the number of AL amyloidosis patients who survive the initial disease phase is expected to grow, resulting in the expansion of patients with chronic organ failure who will require special attention. These patients will be less likely to respond to further anti—plasma cell therapies if they have already achieved a deep response. Options in this cohort of patients include optimization of medical management, organ transplant in eligible patients, and enrollment into clinical trials assessing monoclonal antibodies designated against amyloid. A phase 2/3 multicenter

study using CAEL-101, a monoclonal antibody that showed promise in a phase 1/2 study, is open for enrollment for patients not considered for further anti–plasma cell therapy (NCT04512235; NCT04504825).

CONCLUSION

We provided the reader with a comprehensive evidence-based approach for the diagnosis and management of AL amyloidosis. Given the complexity in the management of this disease and its rarity, referral to a center with expertise in amyloidosis is encouraged when possible to enhance diagnostic aspects and to optimize therapy. Multicenter collaborations at different levels are key to improve quality of evidence in this uncommon yet serious disease.

Abbreviations and Acronyms: **AH** = heavy chain amyloidosis; **AL** = light chain amyloidosis; **ASCT** = autologous stem cell transplant; **BMDex** = bortezomib, melphalan, and dexamethasone; **BU** = Boston University; **CR** = complete response; **CyBorD** = cyclophosphamide, bortezomib, and dexamethasone; **dFLC** = difference between involved and uninvolved immunoglobulin free light chains; **eGFR** = estimated glomerular filtration rate; **ESRD** = end-stage renal disease; **FISH** = fluorescence in situ hybridization; **FLC** = free light chain; **HR** = hematologic response; **iFLC** = involved free light chain; **IMiD** = immunomodulatory drug; **ITT** = intention to treat; **MDex** = melphalan and dexamethasone; **MFC** = multiparametric flow cytometry; **MM** = multiple myeloma; **MRD** = minimal residual disease; **NT-proBNP** = N-terminal brain natriuretic peptide; **OR** = organ response; **OS** = overall survival; **PI** = proteasome inhibitor; **PFS** = progression-free survival; **PR** = partial response; **TRM** = treatment-related mortality; **VGPR** = very good partial response

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