[Category: 2018 Update on Diagnosis, Prognosis, and Treatment]

Immunoglobulin Light Chain Amyloidosis: 2018 Update on Diagnosis, Prognosis, and Treatment

Morie A. Gertz, MD

Author Affiliation: Division of Hematology, Mayo Clinic, Rochester, Minnesota.

Reprints: Morie A. Gertz, MD, Division of Hematology, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905 (gertz.morie@mayo.edu)

Conflict of interest: Author receives honoraria from Prothena, Novartis, Ionis, Sandoz, Amgen, Apellis and Annexon.

Running title: Ig Light Chain (AL) Amyloidosis

Publisher: To expedite proof approval, send proof via e-mail to gertz.morie@mayo.edu.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ajh.25149

Abstract

Disease Overview: Immunoglobulin light chain amyloidosis is a clonal, nonproliferative plasma cell disorder in which fragments of immunoglobulin light or heavy chain are deposited in tissues. Clinical features depend on organs involved but can include restrictive cardiomyopathy, nephrotic syndrome, hepatic dysfunction, peripheral/autonomic neuropathy, and "atypical multiple myeloma."

Diagnosis: Tissue biopsy stained with Congo red demonstrating amyloid deposits with apple-green birefringence is required for diagnosis. Invasive organ biopsy is not required because amyloid deposits can be found in bone marrow, salivary gland or subcutaneous fat aspirate in 85% of patients. Verification that amyloid is composed of immunoglobulin light chains is mandatory. The gold standard is laser capture mass spectroscopy.

Prognosis: N-terminal pro–brain natriuretic peptide (NT-proBNP), serum troponin T, and difference between involved and uninvolved immunoglobulin free light chain values are used to classify patients into four groups of similar size; median survivals are 94.1, 40.3, 14.0, and 5.8 months.

Therapy: All patients with a systemic amyloid syndrome require therapy to prevent deposition of amyloid in other organs and prevent progressive organ failure. Stem cell transplant (SCT) is preferred, but only 20% of patients are eligible. Requirements for safe SCT include systolic blood pressure >90mmHg, troponin T <0.06 ng/mL, age <70 years, and serum creatinine ≤1.7 mg/dL. Nontransplant candidates can be offered melphalan-dexamethasone or cyclophosphamide-bortezomib-dexamethasone. Daratumumab appears to be highly active in AL amyloidosis. Antibodies designed to dissolve existing amyloid deposits are under study.

Future Challenges: Delayed diagnosis remains a major obstacle to initiating effective therapy.

Keywords: amyloidosis; immunoglobulin disorders; infiltrative cardiomyopathy; mass spectroscopy; stem cell transplant

Educational Objectives

Upon completion of this educational activity, participants will be better able to:

- Master recognition of clinical presentations that should raise suspicion of amyloidosis
- Understand simple techniques for confirming the diagnosis and providing material to classify the protein subunit
- Recognize that a tissue diagnosis of amyloidosis does not indicate whether the amyloid is systemic or of immunoglobulin light chain origin
- Understand the roles of the newly introduced chemotherapeutic and investigational antibody regimens for the therapy of light chain amyloidosis

Abbreviations

AL amyloidosis, immunoglobulin light chain amyloidosis

dFLC, difference between involved and uninvolved serum free light chain levels

FLC, free light chain

Ig, immunoglobulin

NT-proBNP, N-terminal pro–brain natriuretic peptide

SCT, stem cell transplant

wtTTR, wild type transthyretin

Introduction

Immunoglobulin light chain (AL) amyloidosis is characterized by a clonal population of bone marrow plasma cells that produces a monoclonal light chain of κ or λ type as either an intact molecule or a fragment [1]. The light chain protein, instead of conforming to the α-helical configuration of most proteins, misfolds and forms a β-pleated sheet [2]. An increase in serum levels of free light chains precedes the development of AL amyloidosis by many years [3]. This insoluble protein deposits in tissues and interferes with organ function. Circulating soluble light chains may also be directly toxic to tissues [4]. The β-pleated sheet configuration is responsible for positive staining with Congo red when viewed under polarized light; this staining is required for the diagnosis of AL amyloidosis [5]. In Sweden, the median survival after diagnosis of AL is three years [6]. It is estimated to have a minimum incidence of 8 per million and is the cause of death in 0.58 of 1,000 recorded deaths [7]. It is responsible for 0.8% of end-stage renal disease [8].

Patient 1: A 70-year-old man was diagnosed with IgG lambda MGUS five years earlier. He was monitored and reassured that his proteins had not changed over time. The monoclonal peak was 1.8 grams/deciliter. The kappa free light chain was 1.36 mg/dL, and the lambda was 22 mg/dL. Over nine months, he developed fatigue and anorexia, early satiety, and a 20-kg weight loss. He underwent coronary angiography that was normal. An endomyocardial biopsy was not done. When evaluated at Mayo Clinic, his liver extended 7.5 cm below the right costal margin; he had 1 g of

proteinuria, all albumin; and his alkaline phosphatase was 2.7 times the upper limit of normal. A fat aspiration was positive for amyloidosis. Comment: The managing hematologist was falsely reassured by the stable M protein that no serious plasma cell dyscrasia was developing [9]. The alkaline phosphatase elevation was overlooked. This is a common presentation of hepatic AL amyloidosis.

Disease Overview

Amyloidosis is particularly difficult to diagnose because no single imaging, blood, or urine test is diagnostic for this disorder [10, 11]. The presenting symptoms often mimic those of more common disorders. The diagnosis of AL amyloidosis should be suspected in any patient with nondiabetic nephrotic syndrome; nonischemic cardiomyopathy with "hypertrophy" on echocardiography [12]; hepatomegaly or increased alkaline phosphatase value with no imaging abnormalities of the liver; chronic inflammatory demyelinating polyneuropathy with a monoclonal protein; or the presence of a monoclonal gammopathy in a patient with unexplained fatigue, edema, weight loss, or paresthesias as illustrated by patient 1 [13]. The presence of proteinuria in a patient with a monoclonal gammopathy may be mistaken for multiple myeloma with cast nephropathy [14]. If specific diagnostic evaluation for amyloidosis is not performed, patients with sensory neuropathy may instead undergo treatment for a chronic inflammatory demyelinating polyneuropathy with a monoclonal protein, receiving plasma exchange and immunoglobulin (Ig) infusions [15]. Some patients with unrecognized cardiac amyloidosis and a bone marrow plasma cell percentage <10% are referred to hematologists with a diagnosis of "atypical multiple myeloma" [16]. The associated fatigue may be

incorrectly ascribed to the mild anemia, the cardiac infiltration goes unrecognized because the patient's ejection fraction is normal (so-called heart failure with preserved ejection fraction), the cardiac silhouette is normal in size [17], and the ventricular thickening is interpreted as hypertrophy rather than infiltration [18]. Patients with monoclonal gammopathy of undetermined significance or smoldering myeloma that are on active monitoring, who present unwell, with weight loss or fatigue, should raise clinical suspicion of amyloidosis. Routine amyloid staining of the bone marrow is not indicated in a typical patient with MGUS or multiple myeloma [19].

Appropriate screening of a patient with a clinical syndrome compatible with AL amyloidosis would include immunofixation of the serum [20], immunofixation of the urine [21], and an Ig free light chain (FLC) assay [22]. The amyloidogenicity of λ Ig light chains is shown in Figure 1, which compares the findings of serum immunofixation in patients with monoclonal gammopathy of undetermined significance, myeloma, and amyloidosis. The high frequency of λ light chain proteinemia is a hallmark of AL amyloidosis. If immunofixation of serum and urine is negative and the Ig FLC (κ:λ) ratio is normal (0.26-1.65), AL amyloidosis is unlikely and further evaluation should not be undertaken, unless the clinical index of suspicion is very high [23]. An algorithm for the evaluation of a patient with suspected amyloidosis is given in Figure 2. Normal studies for immunoglobulin abnormalities do not exclude localized or familial amyloidosis.

If a patient has a compatible clinical syndrome and a light chain abnormality is found, biopsy is required to establish the diagnosis. Biopsy of

the clinically involved organ is generally unnecessary. Renal biopsy [24], endomyocardial biopsy [25], and liver biopsy are expensive, invasive, and increase the risk of post-biopsy hemorrhage. Biopsy of the iliac crest bone marrow [26] combined with abdominal subcutaneous fat aspiration [27] will identify amyloid deposits in 85% of patients with amyloidosis (Table 1). A video demonstrating the technique of fat aspiration is available online [28]. Punch biopsy of the fat [29] provides more material for analysis. Minor salivary gland biopsy is also sensitive in the detection of amyloid if experience with fat aspiration is lacking [30]. If both the fat and the bone marrow stain negative for amyloid, there is still a 15% chance that the patient has amyloidosis, and the appropriate organs should be biopsied if the index of suspicion is high. A positive bone marrow Congo red without a clinical syndrome has only a 2.7% chance of developing amyloidosis. Therefore, routine Congo red staining of the marrow in MGUS or myeloma is not indicated [31]. If amyloid deposits are identified, it is important to determine whether the amyloidosis is localized or systemic. Typical sites for localized amyloidosis include the skin [32], larynx [33], bowel [34, 35] or urinary tract [36], which can include the renal pelvis, ureter, bladder, and urethra. Pulmonary nodules demonstrating amyloid are frequently localized deposits composed of light chains or transthyretin [37]. Deposits found in the colon or stomach, particularly in a polyp or at the edge of an ulcer, can represent degenerative amyloid and may be an incidental endoscopic finding and not reflect systemic AL amyloidosis [38].

Patient 2: A 70-year-old male developed renal biopsy-proven lambda light chain amyloidosis with urinary protein loss of 10.5 g/day. Following stem

cell transplantation, he achieved a complete organ response; 67 months later, at the age of 76, he developed heart failure, and an endomyocardial biopsy demonstrated amyloid. Mass spectroscopy identified the subunit protein as TTR. No mutation was identified. He died of heart failure 39 months later. Comment: This patient with renal AL amyloidosis developed a second form of amyloidosis formerly known as senile cardiac amyloidosis, afflicting predominantly older males. Without mass spectroscopy, it would have been misdiagnosed as relapse of AL amyloidosis in the heart. If a patient has a visceral amyloid syndrome, even if an Ig abnormality is present, it is important to address the possibility that the amyloidosis may be AA amyloidosis (secondary) or TTR (mutant [inherited] or wild type) with an incidental monoclonal gammopathy of undetermined significance [39]. The incidence of MGUS in wild type TTR cardiac amyloidosis is 23% [40]. The light chain origin of an amyloid deposit can be confirmed with immunohistochemistry [41] or an immunogold assay [42]. In AL amyloidosis, a fragment of the light chain is often deposited and may be misfolded so immuno-identification may be equivocal. Mass spectrometry can confirm the amyloid protein composition, and it is considered the standard for typing the protein subunit in amyloid deposits [43]. The technique can be applied to almost any tissue source, including nerves and fat [44, 45], and it can identify heavy chain as well as light chain amyloidosis [46]. Mass spectroscopy is superior to immunohistochemistry in identifying the protein subunit [47]. Of 81 patients with proven transthyretin amyloidosis, 20 had a monoclonal protein, for a positive predictive value of a monoclonal protein of only 74% [48]. Approximately 23% of wtTTR amyloid patients have a MGUS [40]. Among patients with renal biopsy–

proven amyloidosis, 14% have non-immunoglobulin type. Chemotherapy is contraindicated in these patients, so the distinction has important practice implications [49]. A required test panel for patients after histologic diagnosis of AL amyloidosis is given in the Box.

Prognosis

The major determinant of outcome in amyloidosis is the extent of cardiac involvement. The accurate definition of cardiac involvement has evolved over the past three decades. Initially, cardiac involvement meant cardiac failure with cardiomegaly and pleural effusions on the chest radiograph [50]. Clinical cardiac assessment has been supplanted by echocardiography. Wall thickening, a granular sparkling appearance, diastolic relaxation abnormalities, right ventricular dysfunction with valvular thickening, and abnormal echocardiographic strain have all been shown to be associated with prognosis [51]. Cardiac magnetic resonance imaging is increasingly being used for diagnosis and prognosis of cardiac amyloidosis. Late gadolinium enhancement imaging is highly sensitive and specific with images virtually diagnostic for amyloidosis [52]. The use of radionuclide imaging of the heart with Tc PYP or DPD has been found useful in distinguishing AL cardiac amyloidosis (no uptake) from TTR cardiac amyloidosis (2+ or greater uptake) [53].

Tests for serum troponin T and N-terminal pro–brain natriuretic peptide (NT-proBNP) are widely available and are powerful predictors of survival. Survival is also dependent on the size of the plasma cell clone. A staging system for AL amyloidosis is shown in Table 2 [54]. The value of cardiac biomarkers has been validated in patients treated conventionally and those treated with stem cell transplant (SCT) [55]. Several studies have

demonstrated that patients with advanced cardiac disease should be excluded from SCT studies [56]. High troponin T level predicts early mortality from SCT and can be used as an exclusion criterion for this therapy [57]. Patients with advanced heart failure (NT-proBNP>8500 pg/L) also are poor candidates for clinical trials of standard agents [58]. High-sensitivity, fifth-generation cardiac troponin T assays at presentation (median survival is 10.6 months if troponin T levels >77 ng/L) and changes in NT-proBNP levels after chemotherapy are reported to be the best predictors of long-term outcome [59, 60].

An excess of early deaths occur in AL amyloidosis for patients with 10% or greater plasma cells at diagnosis [10]. The Ig FLC level at diagnosis [61], the number of organs involved [62], and the serum uric acid level [63] have all been associated with prognosis. The four-year overall survival from diagnosis improved during each decade of follow-up: survival was 21%, 24%, and 33%, for the periods 1977-1986, 1987-1996, and 1997-2006, respectively (P<.001). However, the one-year mortality rate remained high during the 30-year period (40%), reflecting the failure to diagnose this rare disorder prior to severe end organ damage [64]. Stage of amyloidosis is the most important predictor of outcome. The median survival was not reached in stage I disease; for stages II through IV, median survival was 96.5, 58.2, and 22.2 months, respectively [54]. Table 2 provides the staging criteria. Translocation t(11;14) is associated with an adverse impact on progression-free survival in contrast to myeloma where it has no impact [65]. T(11;14) also predicts a lower response rate to bortezomib-based therapies [65]. Gain 1q, deletion 14q, and deletion 1p appear to have an

adverse prognostic effect [66]. Von Willebrand antigen levels > 230 U/dL appear to define a group with a median survival of two months [67].

For the purpose of uniform reporting, response criteria were developed for hematologic and organ response. Complete response was defined as negative serum and urine immunofixation results, normal FLC ratio, and normal bone marrow. A partial response was defined as a 50% reduction in difference between involved and uninvolved serum free light chain levels (dFLC). A very good partial response was defined as dFLC <40 mg/L. Cardiac response and progression were defined as an increase or decrease of NT-proBNP of 30% and at least 300 ng/L. To qualify as evaluable for response, NT-proBNP levels must be >650 ng/L [68]. Patients with a dFLC <50 mg/L are excluded from most clinical trials because a reliable measurement of 50% reduction does not exist. However these patients have a much better prognosis so ways to include this subgroup in clinical trials of therapy is important [69]. These patients should be held to an endpoint of dFLC<10mg/L. Depression of uninvolved immunoglobulins also has an independent adverse impact on overall survival [70]. In renal amyloidosis, a 75% reduction in proteinuria is associated with markedly prolonged survival [71].

Therapy

Chemotherapy for the treatment of amyloidosis was introduced in 1972 in the form of melphalan and prednisone [72]. The median survival was 12 to 18 months [73]. The goal of chemotherapy is normalization of the involved free light chain [74]. Therapy remained unchanged until the introduction of SCT. The use of SCT in the management of amyloidosis was logical because it could rapidly eradicate the amyloidogenic light chain

produced by the clonal plasma cell populations [75]. Organ response rates of up to 65% have been reported [76]. A prospective randomized study did not demonstrate a survival advantage for patients treated with SCT [77], and a meta-analysis also questioned the value of SCT for amyloidosis [78]. We have reported benefit in a trial comparing transplantation to melphalan dexamethasone [79]. Patients in these studies were not risk-stratified, and some may not have been suitable candidates for transplant [80]. The transplant-related mortality rate has fallen to 2.5% since 2009 [81, 82]. Good outcomes with SCT have been reported for patients with cardiac amyloidosis diagnosed before the onset of advanced congestive heart failure. The hematologic and cardiac response rates were 66% and 41%, respectively, and hematologic response predicted survival [54]. The introduction of plerixafor has made mobilization possible for virtually all eligible patients [83, 84]. Registry data show reduced therapy-related mortality and 77% five-year survival. Outcomes were better at centers performing four AL transplants annually [85].

The ten-year survival after SCT is 25%, and the ten-year survival rate was 53% for patients with a complete response to treatment [86]. Ten-year survival rate of all patients at our center is 43% [87]. Transplant-related mortality rates have decreased from as high as 40% to 4% to 7% in current studies [88, 89]. Extended follow-up of 69 patients enrolled in an SCT trial reported a median survival of 96 months and 120 months for the transplanted cohort [90]. Hematologic relapse occurs at a median of four years. The median survival in patients with hematologic relapse after an initial CR is 8.5 years after relapse [91]. Excluding patients from SCT whose NT-proBNP levels are >5000 pg/mL can reduce therapy-related mortality

rates to 1% [81]. Renal and cardiac organ responses and high complete hematologic response rates have been reported after SCT [92]. No more than 20% to 25% of patients are eligible for transplant. However, response to bortezomib can render one-third of initially transplant-ineligible patients capable of undergoing SCT [93]. Currently, a hematologic response is achievable in 76% of eligible patients, which is complete in 39% [94]. At Mayo Clinic, organ responses have been recorded in 47% of patients [94]. Hematologic response is the strongest predictor of outcome [92]. In an analysis that excluded both early deaths and patients who were unevaluable for response at six months [95], the significance of depth of hematologic response for predicting survival persisted. Remission of proteinuria is not always followed by resolution of amyloid deposits, suggesting that the light chains, rather than amyloid fibrils, directly injure the glomerulus [96]. SCT should remain an important consideration for patients who are eligible to undergo this technique safely.

There is evidence that induction before SCT improves outcomes [97]. Bortezomib followed by SCT resulted in three-year PFS and OS of 58 and 77%, respectively [98]. In a randomized trial of induction versus no induction, the survival rates at 24 months post-treatment start were 95.0% in the bortezomib + HDM/SCT group and 69.4% in the HDM/SCT alone group ($P = 0.03$) [99]. Patients with AL amyloidosis who have more than 10% marrow plasma cells have a poor prognosis and could potentially benefit from induction chemotherapy [100]. Changes in light chain levels are a better predictor of outcome than changes in the intact Ig levels [101].

Conventional Treatment of Amyloidosis

Melphalan and prednisone have been demonstrated to be superior therapy to colchicine in two randomized phase III studies [102-104]. Melphalan and dexamethasone have been combined in the treatment of AL amyloidosis. Of 46 patients who were ineligible for SCT, organ response after treatment with melphalan and dexamethasone was seen in 48% of patients with a low treatment-related mortality rate of only 4%. At six years, the actuarial survival was approximately 50%, and the progression-free survival was 40% [105, 106]. Alkylator-based chemotherapy has been reported to be effective in almost two-thirds of patients [107]. However, two other reports using the identical regimen [105, 106] have shown median survivals of <1.5 years [108, 109]. All of these studies had different patient compositions and had different percentages of patients with advanced disease. When patients with advanced cardiac amyloid involvement are enrolled, early death is common [108, 109]. Cardiac death may not be preventable with implantable cardiac defibrillators [110]. In one report, four pacemakers were placed but did not prevent cardiac decompensation or death in three [111].

Populations of patients with AL amyloidosis are heterogeneous from center to center, with disparate outcomes despite use of the same chemotherapy protocol. Thus, comparison of outcomes across phase II studies is fraught with risks of misinterpretation of data. Outcomes are linked to the proportion of patients with cardiac amyloidosis. It is dangerous to make treatment-based decisions solely on the basis of the outcomes of single-institution phase II trials because patient selection has as much of a role in outcomes as the specifics of therapy [112].

Melphalan plus dexamethasone is still considered a standard treatment for nonstudy, nontransplant intervention because of its low-toxicity profile, its demonstrated ability to produce hematologic responses even in the presence of advanced disease, and the oral availability of both agents [112]. A summary of regimens used in the treatment of amyloidosis is given in Table 3.

Novel Agents in the Treatment of Amyloidosis

Thalidomide

In the first study of thalidomide therapy for AL amyloidosis, 16 patients were treated and no organ responses were seen [113]. In a subsequent study, hematologic responses were reported in 48% of patients, with 19% having complete hematologic responses, but treatment-related toxicity was frequent and the agent was poorly tolerated [114]. Thalidomide has been combined with melphalan and dexamethasone in 22 patients, resulting in 8 hematologic and 4 organ responses [106]. Thalidomide has also been combined with cyclophosphamide and dexamethasone, with a hematologic response rate of 74% and complete response in 21% of patients [115]. Median overall survival from the start of therapy was 41 months, median progression-free survival was 32 months, and treatment-related mortality was 3%. Current recommendations suggest starting thalidomide at a dose not higher than 50 mg. Dose can be increased if tolerated [62]. At Mayo Clinic, this agent is rarely used.

Lenalidomide

Lenalidomide has been combined with dexamethasone in the treatment of AL amyloidosis. Toxicities include cytopenias, rash, fatigue, and cramps [116]. In the first of two published studies, the hematologic

response rate was 41%, and the median response duration and overall survival were 19.2 and 31 months, respectively [58]. In the second study, the response rate was 67% [117]. Of the patients with renal involvement, 41% had a decrease in urinary protein excretion of more than 50% with no decrease in renal function. Response duration and overall survival were not reported [117]. High-risk patients were less likely to respond to lenalidomide.

Lenalidomide has been combined with melphalan and dexamethasone for patients with newly diagnosed AL amyloidosis. In a phase I-II dose-escalation study, the maximum tolerated dose of lenalidomide was 15 mg when combined with melphalan and dexamethasone [118]. Hematologic responses were seen in 58% and were complete in 42%. The two-year, event-free and overall survivals were 54% and 81%, respectively [118]. In a phase 2 study, melphalan, lenalidomide, and dexamethasone produced a 50% response rate, with 7% having a complete response, but the regimen was associated with significant myelosuppression [119]. In a trial of lenalidomide (10 mg), melphalan (0.18 mg/kg for four days), and dexamethasone (40 mg weekly), with 22 of 25 patients having stage II or III cardiac amyloidosis, the one-year survival rate was 58%. Organ responses were seen in 8%. Cardiac arrhythmias were seen in 33% [120].

Lenalidomide has been combined with cyclophosphamide and dexamethasone in 35 patients [121]. The median number of treatment cycles was six. The hematologic response rate was 60% and, in those receiving at least four cycles, the response rate was 87%. The median overall survival was 37.8 months, and similar results were reported with the use of

lenalidomide, cyclophosphamide, and dexamethasone, with an 8% complete response rate and a two-year survival rate of 41%. As salvage therapy in relapsing disease, cyclophosphamide, lenalidomide, and dexamethasone (CRd) can produce a 62% response rate [121-123]. In newly diagnosed patients receiving CRd, a hematologic response rate of 46% and organ response of 46% was reported [124]. In patients with amyloidosis, lenalidomide can frequently worsen kidney function, even for patients whose amyloidosis spares the kidney. Recovery was reported in only 44% [125]. Lenalidomide-treated patients had a higher risk of rising NT-proBNP levels. This is commonly associated with clinical deterioration of the patient. Lenalidomide should not be used as first-line therapy in patients with cardiac involvement [126]. Lenalidomide salvage therapy after bortezomib or melphalan treatment failures has been reported to achieve a hematologic response rate of 41% [127]. Lenalidomide is a legitimate second-line therapy if caution in cardiac amyloid patients is exercised.

Pomalidomide

Pomalidomide, a derivative of thalidomide with structural similarity to both thalidomide and lenalidomide, was administered to 29 patients [128]. Twenty-eight had previously received alkylating agents, as well as autologous SCT in 13, prior lenalidomide or thalidomide in 15, and prior bortezomib in 12. All patients were evaluable for hematologic response with a response rate of 38%. Three patients had very good partial responses, and three and four patients had confirmed and unconfirmed organ responses, respectively [128]. One-year progression-free survival and overall survival rates were 59% and 76%, respectively. Pomalidomide and dexamethasone is a promising therapy for AL amyloidosis. As with lenalidomide, cardiac

amyloidosis patients tolerate this agent poorly with clinical deterioration commonly reported by patients.

Bortezomib

In an early study of bortezomib, 80% of evaluable patients had a hematologic response [129]. A subsequent study of 18 patients demonstrated a hematologic response in 77% with 16% complete responses [130]. A phase I dose-escalation study of bortezomib that specifically excluded use of corticosteroids used two different bortezomib administration schedules: bortezomib administration either 1) on days 1, 4, 8, and 11 every 21 days or 2) on days 1, 8, 15, and 22 every 35 days [131]. Patients with New York Heart Association class III-IV heart disease were excluded. There were no treatment-related deaths. Hematologic responses were seen in 50% of patients, 20% of which were complete responses; median time to response was 1.2 months. Bortezomib has been reported to successfully improve cardiac function in AL amyloidosis [132]. Combination bortezomib and dexamethasone has been used after SCT to improve the depth of response [133]. Nineteen patients received post-transplant bortezomib and dexamethasone, and 67% achieved a complete response with organ responses in 60%. Data from 33 national centers were combined in another study, reporting on 94 patients receiving bortezomib with or without dexamethasone [134]. Hematologic responses were seen in 71%, with 25% having complete responses. A cardiac response was seen in 29% of patients. The NT-proBNP level predicted survival. In another study, the combination of bortezomib-dexamethasone was given to 26 patients; 18 received this as first-line therapy [135]. The overall response rate was 54%, with 31% complete responses. The median time to response was 7.5 weeks [135]. A

survey of European centers, with 428 evaluable patients, reported that bortezomib therapy achieved a lower dFLC at completion of therapy compared with treatment with cyclophosphamide-thalidomide-dexamethasone, melphalan and dexamethasone, SCT, and cyclophosphamide-lenalidomide-dexamethasone [136].

Bortezomib has been combined with cyclophosphamide and dexamethasone (Cybor-d) and represents our preferred treatment in non-transplant-eligible patients not on a trial. In one study [137], 17 patients (10 therapy naïve) achieved a response rate of 94% with 71% achieving a complete response. Three subsequently became transplant-eligible. A second cohort of 43 patients achieved a hematologic response rate of 81% with 42% achieving a complete response [138]. Two-year progression-free survival was 67% for newly diagnosed patients. In a European collaborative study, 230 patients were treated frontline with CyBorD. Overall hematologic response rate was 60%; and in the 201 patients with measurable disease, it was 62% with 43% achieving at least very good partial response (VGPR). Cardiac response was reached in 17% of patients and renal response in 25% of patients [139]. It is not proven that addition of cyclophosphamide to bortezomib-dexamethasone significantly impacts response or survival [140]. Combinations of novel agents are being reported. In one study, seven of nine in a case series received bortezomib, cyclophosphamide, or lenalidomide/thalidomide, and dexamethasone. Hematologic and organ response was seen in 89% and 78% of patients, respectively. A survey of European centers using Cybor-d in newly diagnosed patients reported a response rate of 60% but a median survival of advanced cardiac patients of only seven months [139]. Bortezomib-melphalan-prednisone (VMP) in

newly diagnosed AL produces an 84% hematologic response rate [141]. Unfortunately, neuropathy was reported in 44% [142]. The non-neurotoxic proteosome inhibitor Ixazomib in relapse-refractory AL produced hematologic response in 52% and organ response in 56% at a dose of 4 mg by mouth weekly [143]. Bendamustine is currently being explored for its activity in AL amyloidosis [144]. There has been one report of Venetoclax therapy for amyloidosis with t(11;14) [145].

Daratumumab

Daratumumab is a highly effective anti-plasma cell therapy producing deep responses, making it an ideal agent for the treatment of AL amyloidosis. Stanford University [146] conducted a retrospective review of all patients with AL amyloidosis treated with daratumumab over a 12-month period. Cardiac and renal involvement was present in 72% and 68% of patients, respectively. Daratumumab was administered at the standard schedule intravenously at a dose of 16 mg/kg weekly for eight weeks, followed by every other week for eight doses, and then every four weeks, thereafter. The responses were rapid and impressive. The hematologic response rate was 76% with 36% achieving a complete response (CR) and 24% achieving a very good partial response (VGPR) with a median time to deepest response of one month. Daratumumab-based therapies in 41 patients (20 receiving monotherapy and 21 receiving combination therapy) with relapsed or refractory AL amyloidosis were reported from Mayo Clinic [147]. After a median follow-up of 7.5 months, hematologic response rate in 30 patients was 80%. Cardiac response was seen in 8 (33%) and renal response in 6 (32%) patients. The median PFS was 16.2 months. Median OS

for the cohort from initiation of daratumumab-based therapy has not been reached.

Figures 3A&B shows chemotherapy algorithms recommended for patients with newly diagnosed AL amyloidosis (stratified by transplant eligibility). For patients who achieve a complete hematologic response, kidney transplantation can be successful (80% graft survival at 42 months) [148]. Renal transplantation is feasible in AL [149]. Selection should exclude patients with extrarenal amyloid deposition, and the underlying clonal plasma cell disorder ideally should be controlled [150]. Median graft survival of 8.9 years is reported when amyloid precursor protein production is reduced. In a registry series [8], 46 patients received renal allografts. Five- and ten-year graft survival rates were 45% and 26%, respectively. Amyloid recurrence was proven in 16%.A summary of non-transplant therapies is given. (Table 3).

Cardiac transplantation can also be performed, but strict control of the plasma cell population is required to prevent subsequent amyloid deposition. Nine AL patients are all alive with only one amyloid recurrence in the graft [151].

Antibodies

Three trials of antibodies are under way. An antibody to SAP, dezamizumab, with pretreatment with Miridesap resulted in improved imaging with SAP scans and decreased liver stiffness as measured with the use of elastography NCT01777243 [152, 153]. An antibody to a cryptic epitope of the fibril was reported to produce both renal and cardiac responses in patients following anti plasma cell chemotherapy NCT02312206 [154]. Prothena recently announced the discontinuation of

the development of NEO001 for AL Amyloidosis because the Phase 2b PRONTO study did not meet its primary or secondary endpoints. In addition the Phase 3 VITAL study was discontinued based on futility analysis.
The fibril-reactive mAb 11-1F4, when labeled with iodine-124 was shown to bind AL amyloid in patients by using PET/CT imaging and is being studied NCT02245867.

Conclusion

When AL amyloidosis is diagnosed before the development of advanced cardiomyopathy, patients can achieve both hematologic and organ responses after chemotherapy, which translates into prolonged survival. The best predictor of organ response is a deep hematologic response [155]. A patient with a compatible syndrome that suggests amyloidosis should have testing with immunofixation and FLC assessment followed by bone marrow and fat biopsies to establish the diagnosis. Once the amyloidosis is confirmed to be of light chain origin, patients should be considered for SCT (only a minority are eligible) or trials of systemic chemotherapy. Active agents include corticosteroids (dexamethasone, prednisone), alkylating agents (melphalan, cyclophosphamide), immunomodulatory drugs (thalidomide, lenalidomide), proteasome inhibitors (bortezomib), and daratumumab. Antibodies against amyloid deposits are a potential new therapeutic strategy.

References

1. Zhou P, Comenzo RL, Olshen AB, et al. CD32B is highly expressed on clonal plasma cells from patients with systemic light-chain amyloidosis and provides a target for monoclonal antibody-based therapy. Blood 2008;111:3403-3406.

2. Bhat A, Selmi C, Naguwa SM, et al. Currents concepts on the immunopathology of amyloidosis. Clin Rev Allergy Immunol 2010;38:97-106.

3. Weiss BM, Hebreo J, Cordaro DV, et al. Increased serum free light chains precede the presentation of immunoglobulin light chain amyloidosis. J Clin Oncol 2014;32:2699-2704.

4. Imperlini E, Gnecchi M, Rognoni P, et al. Proteotoxicity in cardiac amyloidosis: amyloidogenic light chains affect the levels of intracellular proteins in human heart cells. Sci Rep 2017;7:15661.

5. Picken MM. Amyloidosis-where are we now and where are we heading? Arch Pathol Lab Med 2010;134:545-551.

6. Hemminki K, Li X, Forsti A, et al. Incidence and survival in non-hereditary amyloidosis in Sweden. BMC Public Health 2012;12:974.

7. Pinney JH, Smith CJ, Taube JB, et al. Systemic amyloidosis in England: an epidemiological study. Br J Haematol 2013;161:525-532.

8. Tang W, McDonald SP, Hawley CM, et al. End-stage renal failure due to amyloidosis: outcomes in 490 ANZDATA registry cases. Nephrol Dial Transplant 2013;28:455-461.

9. McCausland KL, White MK, Guthrie SD, et al. Light Chain (AL) Amyloidosis: The Journey to Diagnosis. Patient 2018;11:207-216.

10. Chee CE, Lacy MQ, Dogan A, et al. Pitfalls in the diagnosis of primary amyloidosis. Clin Lymphoma Myeloma Leuk 2010;10:177-180.

11. Chen W, Dilsizian V. Molecular imaging of amyloidosis: will the heart be the next target after the brain? Curr Cardiol Rep 2012;14:226-233.

12. Mabru M, Dacher JN, Bauer F. Left ventricular hypertrophy: cardiac magnetic resonance may help differentiate amyloidosis from hypertrophic cardiomyopathy. Arch Cardiovasc Dis 2010;103:55-56.

13. Perfetto F, Moggi-Pignone A, Livi R, et al. Systemic amyloidosis: a challenge for the rheumatologist. Nat Rev Rheumatol 2010;6:417-429.

14. Stratta P, Gravellone L, Cena T, et al. Renal outcome and monoclonal immunoglobulin deposition disease in 289 old patients with blood cell dyscrasias: a single center experience. Crit Rev Oncol Hematol 2011;79:31-42.

15. England JD, Gronseth GS, Franklin G, et al. Practice parameter: the evaluation of distal symmetric polyneuropathy: the role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. PM R 2009;1:14-22.

16. Sedaghat D, Zakir RM, Choe J, et al. Cardiac amyloidosis in a patient with multiple myeloma: a case report and review of literature. J Clin Ultrasound 2009;37:179-184.

17. Tsang W, Lang RM. Echocardiographic evaluation of cardiac amyloid. Curr Cardiol Rep 2010;12:272-276.

18. Cheng AS, Banning AP, Mitchell AR, et al. Cardiac changes in systemic amyloidosis: visualisation by magnetic resonance imaging. Int J Cardiol 2006;113:E21-23.

19. Siragusa S, Morice W, Gertz MA, et al. Asymptomatic immunoglobulin light chain amyloidosis (AL) at the time of diagnostic bone marrow biopsy in newly diagnosed patients with multiple myeloma and smoldering myeloma. A series of 144 cases and a review of the literature. Ann Hematol 2011;90:101-106.

20. Katzmann JA. Screening panels for monoclonal gammopathies: time to change. Clin Biochem Rev 2009;30:105-111.

21. Shaheen SP, Levinson SS. Serum free light chain analysis may miss monoclonal light chains that urine immunofixation electrophoreses would detect. Clin Chim Acta 2009;406:162-166.

22. Dispenzieri A, Kyle R, Merlini G, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia 2009;23:215-224.

23. Palladini G, Russo P, Bosoni T, et al. Identification of amyloidogenic light chains requires the combination of serum-free light chain assay with immunofixation of serum and urine. Clin Chem 2009;55:499-504.

24. von Hutten H, Mihatsch M, Lobeck H, et al. Prevalence and origin of amyloid in kidney biopsies. Am J Surg Pathol 2009;33:1198-1205.

25. Kieninger B, Eriksson M, Kandolf R, et al. Amyloid in endomyocardial biopsies. Virchows Arch 2010;456:523-532.

26. Petruzziello F, Zeppa P, Catalano L, et al. Amyloid in bone marrow smears of patients affected by multiple myeloma. Ann Hematol 2010;89:469-474.

27. van G, II, Hazenberg BP, Bijzet J, et al. Amyloid load in fat tissue reflects disease severity and predicts survival in amyloidosis. Arthritis Care Res (Hoboken) 2010;62:296-301.

28. Trafton W, Libbey C. Abdominal fat tissue aspirate procedure [Internet]. Boston (MA): Boston University School of Medicine [cited 2014 Aug 5]. http://www.youtube.com/watch?v=5ctYTmxd9gQ.; 2014.

29. Guidelli GM, Bardelli M, Selvi E, et al. Punch biopsy for fat tissue collection in amyloidosis: is it time to stop needle aspiration? Rheumatology (Oxford) 2015;54:2109-2111.

30. Suzuki T, Kusumoto S, Yamashita T, et al. Labial salivary gland biopsy for diagnosing immunoglobulin light chain amyloidosis: a retrospective analysis. Ann Hematol 2016;95:279-285.

31. Chakraborty R, Gertz MA, Dispenzieri A, et al. Natural history of amyloidosis isolated to fat and bone marrow aspirate. Br J Haematol 2017;179:170-172.

32. Dahdah MJ, Kurban M, Kibbi AG, et al. Primary localized cutaneous amyloidosis: a sign of immune dysregulation? Int J Dermatol 2009;48:419-421.

33. Gallivan GJ, Gallivan HK. Laryngeal amyloidosis causing hoarseness and airway obstruction. J Voice 2010;24:235-239.

34. Kagawa M, Fujino Y, Muguruma N, et al. Localized amyloidosis of the stomach mimicking a superficial gastric cancer. Clin J Gastroenterol 2016;9:109-113.

35. Antonini F, Goteri G, Macarri G. Bleeding localized amyloidosis of the colon. Dig Liver Dis 2014;46:e13.

36. Javed A, Canales BK, Maclennan GT. Bladder amyloidosis. J Urol 2010;183:2388-2389.

37. Roden AC, Aubry MC, Zhang K, et al. Nodular senile pulmonary amyloidosis: a unique case confirmed by immunohistochemistry, mass spectrometry, and genetic study. Hum Pathol 2010;41:1040-1045.

38. Biewend ML, Menke DM, Calamia KT. The spectrum of localized amyloidosis: a case series of 20 patients and review of the literature. Amyloid 2006;13:135-142.

39. Comenzo RL, Zhou P, Fleisher M, et al. Seeking confidence in the diagnosis of systemic AL (Ig light-chain) amyloidosis: patients can have both monoclonal gammopathies and hereditary amyloid proteins. Blood 2006;107:3489-3491.

40. Geller HI, Singh A, Mirto TM, et al. Prevalence of Monoclonal Gammopathy in Wild-Type Transthyretin Amyloidosis. Mayo Clin Proc 2017;92:1800-1805.

41. Linke RP, Oos R, Wiegel NM, et al. Classification of amyloidosis: misdiagnosing by way of incomplete immunohistochemistry and how to prevent it. Acta Histochem 2006;108:197-208.

42. Gruys E, Ultee A, Upragarin N. Glycosaminoglycans are part of amyloid fibrils: ultrastructural evidence in avian AA amyloid stained with cuprolinic blue and labeled with immunogold. Amyloid 2006;13:13-19.

43. Vrana JA, Gamez JD, Madden BJ, et al. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood 2009;114:4957-4959.

44. Brambilla F, Lavatelli F, Di Silvestre D, et al. Reliable typing of systemic amyloidoses through proteomic analysis of subcutaneous adipose tissue. Blood 2012;119:1844-1847.

45. Klein CJ, Vrana JA, Theis JD, et al. Mass spectrometric-based proteomic analysis of amyloid neuropathy type in nerve tissue. Arch Neurol 2011;68:195-199.

46. Sethi S, Theis JD, Leung N, et al. Mass spectrometry-based proteomic diagnosis of renal immunoglobulin heavy chain amyloidosis. Clin J Am Soc Nephrol 2010;5:2180-2187.

47. Gilbertson JA, Theis JD, Vrana JA, et al. A comparison of immunohistochemistry and mass spectrometry for determining the amyloid fibril protein from formalin-fixed biopsy tissue. J Clin Pathol 2015;68:314-317.

48. Maleszewski JJ, Murray DL, Dispenzieri A, et al. Relationship between monoclonal gammopathy and cardiac amyloid type. Cardiovasc Pathol 2013;22:189-194.

49. Said SM, Sethi S, Valeri AM, et al. Renal amyloidosis: origin and clinicopathologic correlations of 474 recent cases. Clin J Am Soc Nephrol 2013;8:1515-1523.

50. Desai HV, Aronow WS, Peterson SJ, et al. Cardiac amyloidosis: approaches to diagnosis and management. Cardiol Rev 2010;18:1-11.

51. Koyama J, Falk RH. Prognostic significance of strain Doppler imaging in light-chain amyloidosis. JACC Cardiovasc Imaging 2010;3:333-342.

52. Suesse S, Blueml M, Pragst F. Effect of the analyzed hair length on fatty acid ethyl ester (FAEE) concentrations in hair--is there congruence of cut-offs for 0-3 and 0-6 cm hair segments? Forensic Sci Int 2015;249:1-5.

53. Harb SC, Haq M, Flood K, et al. National patterns in imaging utilization for diagnosis of cardiac amyloidosis: A focus on Tc99m-pyrophosphate scintigraphy. J Nucl Cardiol 2016.

54. Madan S, Kumar SK, Dispenzieri A, et al. High-dose melphalan and peripheral blood stem cell transplantation for light-chain amyloidosis with cardiac involvement. Blood 2012;119:1117-1122.

55. 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;104:1881-1887.

56. Kumar S, Dispenzieri A, Gertz MA. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med 2008;358:91; author reply 92-93.

57. 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;49:36-41.

58. Dispenzieri A, Lacy MQ, Zeldenrust SR, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. Blood 2007;109:465-470.

59. Ishiguro K, Hayashi T, Igarashi T, et al. Decrease of B-type natriuretic peptide to less than 200 pg/mL predicts longer survival in cardiac immunoglobulin light chain amyloidosis. Int J Hematol 2015;102:200-204.

60. Palladini G, Merlini G. Uniform risk-stratification and response criteria are paving the way to evidence-based treatment of AL amyloidosis. Oncology (Williston Park) 2011;25:633, 637-638.

61. 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;116:5126-5129.

62. Gertz MA, Zeldenrust SR. Treatment of immunoglobulin light chain amyloidosis. Curr Hematol Malig Rep 2009;4:91-98.

63. Kumar S, Dispenzieri A, Lacy MQ, et al. Serum uric acid: novel prognostic factor in primary systemic amyloidosis. Mayo Clin Proc 2008;83:297-303.

64. Kumar SK, Gertz MA, Lacy MQ, et al. Recent improvements in survival in primary systemic amyloidosis and the importance of an early mortality risk score. Mayo Clin Proc 2011;86:12-18.

65. Bochtler T, Hegenbart U, Kunz C, et al. Translocation t(11;14) is associated with adverse outcome in patients with newly diagnosed AL amyloidosis when treated with bortezomib-based regimens. J Clin Oncol 2015;33:1371-1378.

66. Granzow M, Hegenbart U, Hinderhofer K, et al. Novel recurrent chromosomal aberrations detected in clonal plasma cells of light chain amyloidosis patients show potential adverse prognostic effect: first results from a genome-wide copy number array analysis. Haematologica 2017;102:1281-1290.

67. Kastritis E, Papassotiriou I, Terpos E, et al. Clinical and prognostic significance of serum levels of von Willebrand factor and ADAMTS-13 antigens in AL amyloidosis. Blood 2016;128:405-409.

68. 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;30:4541-4549.

69. Dittrich T, Bochtler T, Kimmich C, et al. AL amyloidosis patients with low amyloidogenic free light chain levels at first diagnosis have an excellent prognosis. Blood 2017;130:632-642.

70. Muchtar E, Dispenzieri A, Kumar SK, et al. Immunoparesis in newly diagnosed AL amyloidosis is a marker for response and survival. Leukemia 2017;31:92-99.

71. Leung N, Glavey SV, Kumar S, et al. A detailed evaluation of the current renal response criteria in AL amyloidosis: is it time for a revision? Haematologica 2013;98:988-992.

72. Jones NF, Hilton PJ, Tighe JR, et al. Treatment of "primary" renal amyloidosis with melphalan. Lancet 1972;2:616-619.

73. Kyle RA, Bayrd ED. Amyloidosis: review of 236 cases. Medicine (Baltimore) 1975;54:271-299.

74. Tandon N, Sidana S, Dispenzieri A, et al. Impact of involved free light chain (FLC) levels in patients achieving normal FLC ratio after initial therapy in light chain amyloidosis (AL). Am J Hematol 2018;93:17-22.

75. Comenzo RL, Vosburgh E, Simms RW, et al. Dose-intensive melphalan with blood stem cell support for the treatment of AL amyloidosis: one-year follow-up in five patients. Blood 1996;88:2801-2806.

76. Dispenzieri A, Merlini G, Comenzo RL. Amyloidosis 2008 BMT Tandem Meetings (February 13-17, San Diego). Biol Blood Marrow Transplant 2008;14:6-11.

77. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med 2007;357:1083-1093.

78. Mhaskar R, Kumar A, Behera M, et al. Role of high-dose chemotherapy and autologous hematopoietic cell transplantation in primary systemic amyloidosis: a systematic review. Biol Blood Marrow Transplant 2009;15:893-902.

79. Gertz MA, Lacy MQ, Dispenzieri A, et al. Stem cell transplantation compared with melphalan plus dexamethasone in the treatment of immunoglobulin light-chain amyloidosis. Cancer 2016;122:2197-2205.

80. Mehta J, Dispenzieri A, Gertz MA. High-dose chemotherapy with autotransplantation in AL amyloidosis: a flawed meta-analysis. Biol Blood Marrow Transplant 2010;16:138-140; author reply 140-131.

81. 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;48:557-561.

82. Sidiqi MH, Aljama MA, Buadi FK, et al. Stem Cell Transplantation for Light Chain Amyloidosis: Decreased Early Mortality Over Time. J Clin Oncol 2018;36:1323-1329.

83. Dhakal B, Strouse C, D'Souza A, et al. Plerixafor and abbreviated-course granulocyte colony-stimulating factor for mobilizing hematopoietic progenitor cells in light chain amyloidosis. Biol Blood Marrow Transplant 2014;20:1926-1931.

84. Dunn D, Vikas P, Jagasia M, et al. Plerixafor in AL amyloidosis: improved graft composition and faster lymphocyte recovery after auto-SCT

in patient with end-stage renal-disease. Bone Marrow Transplant 2012;47:1136-1137.

85. Lachapelle P, Blain L, Quigley MG, et al. The effect of diphenylhydantoin on the electroretinogram. Doc Ophthalmol 1989;73:359-368.

86. Sanchorawala V, Skinner M, Quillen K, et al. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. Blood 2007;110:3561-3563.

87. Cordes S, Dispenzieri A, Lacy MQ, et al. Ten-year survival after autologous stem cell transplantation for immunoglobulin light chain amyloidosis. Cancer 2012;118:6105-6109.

88. Gertz MA, Lacy MQ, Dispenzieri A, et al. Trends in day 100 and 2-year survival after auto-SCT for AL amyloidosis: outcomes before and after 2006. Bone Marrow Transplant 2011;46:970-975.

89. Tsai SB, Seldin DC, Quillen K, et al. High-dose melphalan and stem cell transplantation for patients with AL amyloidosis: trends in treatment-related mortality over the past 17 years at a single referral center. Blood 2012;120:4445-4446.

90. Hazenberg BP, Croockewit A, van der Holt B, et al. Extended follow up of high-dose melphalan and autologous stem cell transplantation after vincristine, doxorubicin, dexamethasone induction in amyloid light chain amyloidosis of the prospective phase II HOVON-41 study by the Dutch-Belgian Co-operative Trial Group for Hematology Oncology. Haematologica 2015;100:677-682.

91. Browning S, Quillen K, Sloan JM, et al. Hematologic relapse in AL amyloidosis after high-dose melphalan and stem cell transplantation. Blood 2017;130:1383-1386.

92. Gertz MA, Lacy MQ, Dispenzieri A, et al. Effect of hematologic response on outcome of patients undergoing transplantation for primary amyloidosis: importance of achieving a complete response. Haematologica 2007;92:1415-1418.

93. Cornell RF, Zhong X, Arce-Lara C, et al. Bortezomib-based induction for transplant ineligible AL amyloidosis and feasibility of later transplantation. Bone Marrow Transplant 2015;50:914-917.

94. Gertz MA, Lacy MQ, Dispenzieri A, et al. Transplantation for amyloidosis. Curr Opin Oncol 2007;19:136-141.

95. Gertz MA, Lacy MQ, Dispenzieri A, et al. Autologous stem cell transplant for immunoglobulin light chain amyloidosis: a status report. Leuk Lymphoma 2010;51:2181-2187.

96. Okuyama H, Yamaya H, Fukusima T, et al. A patient with persistent renal AL amyloid deposition after clinical remission by HDM/SCT therapy. Clin Nephrol 2013;79:233-236.

97. Madan S, Kumar S, Lacy M, et al. Pre-stem cell transplant induction therapy does not affect post-transplant survival in light chain (AL) amyloidosis [abstract 370]. Blood 2010;116.

98. Scott EC, Heitner SB, Dibb W, et al. Induction bortezomib in Al amyloidosis followed by high dose melphalan and autologous stem cell transplantation: a single institution retrospective study. Clin Lymphoma Myeloma Leuk 2014;14:424-430 e421.

99. 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.

100. 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;31:4319-4324.

101. Kumar SK, Dispenzieri A, Lacy MQ, et al. Changes in serum-free light chain rather than intact monoclonal immunoglobulin levels predicts outcome following therapy in primary amyloidosis. Am J Hematol 2011;86:251-255.

102. Kyle RA, Gertz MA, Greipp PR, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med 1997;336:1202-1207.

103. Skinner M, Anderson J, Simms R, et al. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. Am J Med 1996;100:290-298.

104. Sanchorawala V, Wright DG, Seldin DC, et al. Low-dose continuous oral melphalan for the treatment of primary systemic (AL) amyloidosis. Br J Haematol 2002;117:886-889.

105. Palladini G, Perfetti V, Obici L, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. Blood 2004;103:2936-2938.

106. 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;88:347-350.

107. Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. J Clin Oncol 2011;29:1924-1933.

108. 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;116:522-528.

109. Lebovic D, Hoffman J, Levine BM, et al. Predictors of survival in patients with systemic light-chain amyloidosis and cardiac involvement initially ineligible for stem cell transplantation and treated with oral melphalan and dexamethasone. Br J Haematol 2008;143:369-373.

110. Lin G, Dispenzieri A, Kyle R, et al. Implantable cardioverter defibrillators in patients with cardiac amyloidosis. J Cardiovasc Electrophysiol 2013;24:793-798.

111. Sayed RH, Rogers D, Khan F, et al. A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis. Eur Heart J 2015;36:1098-1105.

112. Gertz MA. I don't know how to treat amyloidosis. Blood 2010;116:507-508.

113. Blade J, Rosinol L. Thalidomide: a step forward in the treatment of malignant monoclonal gammopathies. Clin Lymphoma 2003;3:247-248.

114. Dispenzieri A, Lacy MQ, Rajkumar SV, et al. Poor tolerance to high doses of thalidomide in patients with primary systemic amyloidosis. Amyloid 2003;10:257-261.

115. Wechalekar AD, Goodman HJ, Lachmann HJ, et al. Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. Blood 2007;109:457-464.

116. Sviggum HP, Davis MD, Rajkumar SV, et al. Dermatologic adverse effects of lenalidomide therapy for amyloidosis and multiple myeloma. Arch Dermatol 2006;142:1298-1302.

117. 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;109:492-496.

118. Moreau P, Jaccard A, Benboubker L, et al. Lenalidomide in combination with melphalan and dexamethasone in patients with newly diagnosed AL amyloidosis: a multicenter phase 1/2 dose-escalation study. Blood 2010;116:4777-4782.

119. Sanchorawala V, Patel JM, Sloan JM, et al. Melphalan, lenalidomide and dexamethasone for the treatment of immunoglobulin light chain amyloidosis: results of a phase II trial. Haematologica 2013;98:789-792.

120. Dinner S, Witteles W, Afghahi A, et al. Lenalidomide, melphalan and dexamethasone in a population of patients with immunoglobulin light chain amyloidosis with high rates of advanced cardiac involvement. Haematologica 2013;98:1593-1599.

121. Kumar SK, Hayman SR, Buadi FK, et al. Lenalidomide, cyclophosphamide, and dexamethasone (CRd) for light-chain amyloidosis: long-term results from a phase 2 trial. Blood 2012;119:4860-4867.

122. 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;119:5384-5390.

123. 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;98:433-436.

124. Cibeira MT, Oriol A, Lahuerta JJ, et al. A phase II trial of lenalidomide, dexamethasone and cyclophosphamide for newly diagnosed patients with systemic immunoglobulin light chain amyloidosis. Br J Haematol 2015;170:804-813.

125. Specter R, Sanchorawala V, Seldin DC, et al. Kidney dysfunction during lenalidomide treatment for AL amyloidosis. Nephrol Dial Transplant 2011;26:881-886.

126. 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;85:757-759.

127. 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;91:89-92.

128. Dispenzieri A, Buadi F, Laumann K, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. Blood 2012;119:5397-5404.

129. Wechalekar AD, Lachmann HJ, Offer M, et al. Efficacy of bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease. Haematologica 2008;93:295-298.

130. Sitia R, Palladini G, Merlini G. Bortezomib in the treatment of AL amyloidosis: targeted therapy? Haematologica 2007;92:1302-1307.

131. 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;114:1489-1497.

132. Tamaki H, Naito Y, Lee-Kawabata M, et al. Sustained improvement in cardiac function with persistent amyloid deposition in a patient with multiple myeloma-associated cardiac amyloidosis treated with bortezomib. Int J Hematol 2010;92:655-658.

133. 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;27:823-828.

134. Kastritis E, Wechalekar AD, Dimopoulos MA, et al. Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis. J Clin Oncol 2010;28:1031-1037.

135. Lamm W, Willenbacher W, Lang A, et al. Efficacy of the combination of bortezomib and dexamethasone in systemic AL amyloidosis. Ann Hematol 2011;90:201-206.

136. 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;121:3420-3427.

137. 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;119:4391-4394.

138. Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal

response rates and prolonged progression-free survival. Blood 2012;119:4387-4390.

139. Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood 2015;126:612-615.

140. Kastritis E, Gavriatopoulou M, Roussou M, et al. Addition of cyclophosphamide and higher doses of dexamethasone do not improve outcomes of patients with AL amyloidosis treated with bortezomib. Blood Cancer J 2017;7:e570.

141. Lee JY, Lim SH, Kim SJ, et al. Bortezomib, melphalan, and prednisolone combination chemotherapy for newly diagnosed light chain (AL) amyloidosis. Amyloid 2014;21:261-266.

142. Chari A, Barley K, Jagannath S, et al. Safety and efficacy of triplet regimens in newly diagnosed light chain amyloidosis. Clin Lymphoma Myeloma Leuk 2013;13:55-61.

143. Sanchorawala V, Palladini G, Kukreti V, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. Blood 2017;130:597-605.

144. Columbia University. Bendamustine and dexamethasone in patients with relapsed AL amyloidosis. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [2014 Aug 5]. Available from: http://clinicaltrials.gov/ct2/show/NCT01222260?term=nct01222260&rank=1 NLM Identifier: NCT01222260. . 2014.

145. Leung N, Thome SD, Dispenzieri A. Venetoclax induced a complete response in a patient with immunoglobulin light chain amyloidosis plateaued

on cyclophosphamide, bortezomib and dexamethasone. Haematologica 2018;103:e135-e137.

146. Kaufman GP, Schrier SL, Lafayette RA, et al. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood 2017;130:900-902.

147. Abeykoon JP, Kumar S, Dispenzieri A, et al. Daratumumab-based therapies in patients with AL amyloidosis. The XVIth International Symposium on Amyloidosis, March 26-29; Kumamoto, Japan 2018. 2018.

148. Herrmann SM, Gertz MA, Stegall MD, et al. Long-term outcomes of patients with light chain amyloidosis (AL) after renal transplantation with or without stem cell transplantation. Nephrol Dial Transplant 2011;26:2032-2036.

149. Leung N, Griffin MD, Dispenzieri A, et al. Living donor kidney and autologous stem cell transplantation for primary systemic amyloidosis (AL) with predominant renal involvement. Am J Transplant 2005;5:1660-1670.

150. Pinney JH, Lachmann HJ, Sattianayagam PT, et al. Renal transplantation in systemic amyloidosis-importance of amyloid fibril type and precursor protein abundance. Am J Transplant 2013;13:433-441.

151. Davis MK, Kale P, Liedtke M, et al. Outcomes after heart transplantation for amyloid cardiomyopathy in the modern era. Am J Transplant 2015;15:650-658.

152. Richards DB, Cookson LM, Berges AC, et al. Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component. N Engl J Med 2015;373:1106-1114.

153. Richards DB, Cookson LM, Barton SV, et al. Repeat doses of antibody to serum amyloid P component clear amyloid deposits in patients with systemic amyloidosis. Sci Transl Med 2018;10.
154. Gertz MA, Landau H, Comenzo RL, et al. First-in-Human Phase I/II Study of NEOD001 in Patients With Light Chain Amyloidosis and Persistent Organ Dysfunction. J Clin Oncol 2016;34:1097-1103.
155. Pinney JH, Lachmann HJ, Bansi L, et al. Outcome in renal Al amyloidosis after chemotherapy. J Clin Oncol 2011;29:674-681.

Legends

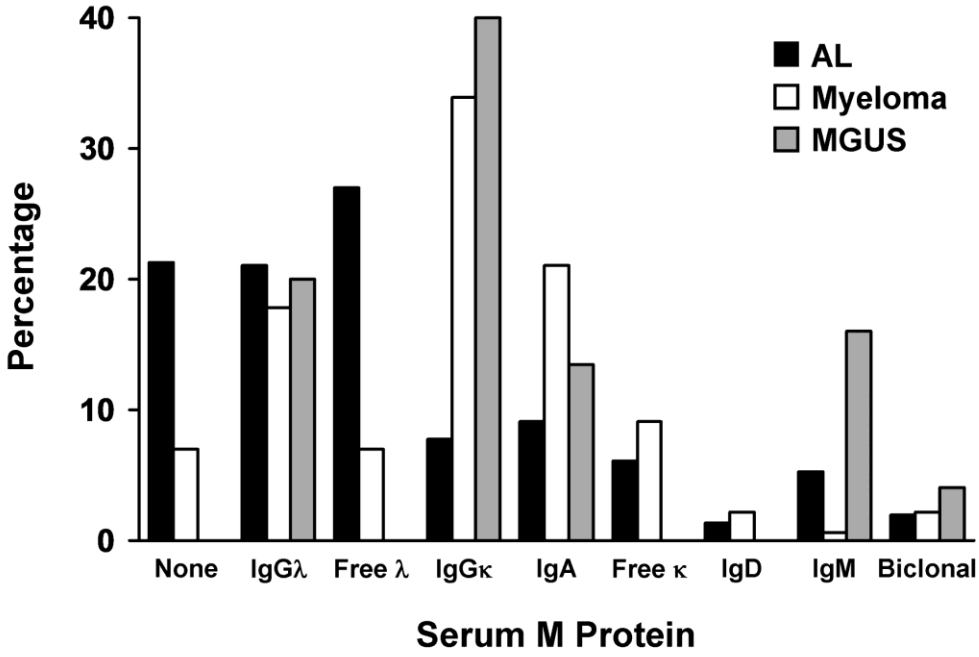


Figure 1. Types of Serum M Proteins Found on Immunofixation Results. The percentage of each type of M protein is shown in samples from patients with MGUS (21), myeloma (22), and AL amyloidosis (23). The ratio of λ:κ light chain in patients with AL amyloidosis is 3.8. AL amyloidosis indicates immunoglobulin light chain amyloidosis; Ig, immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance.

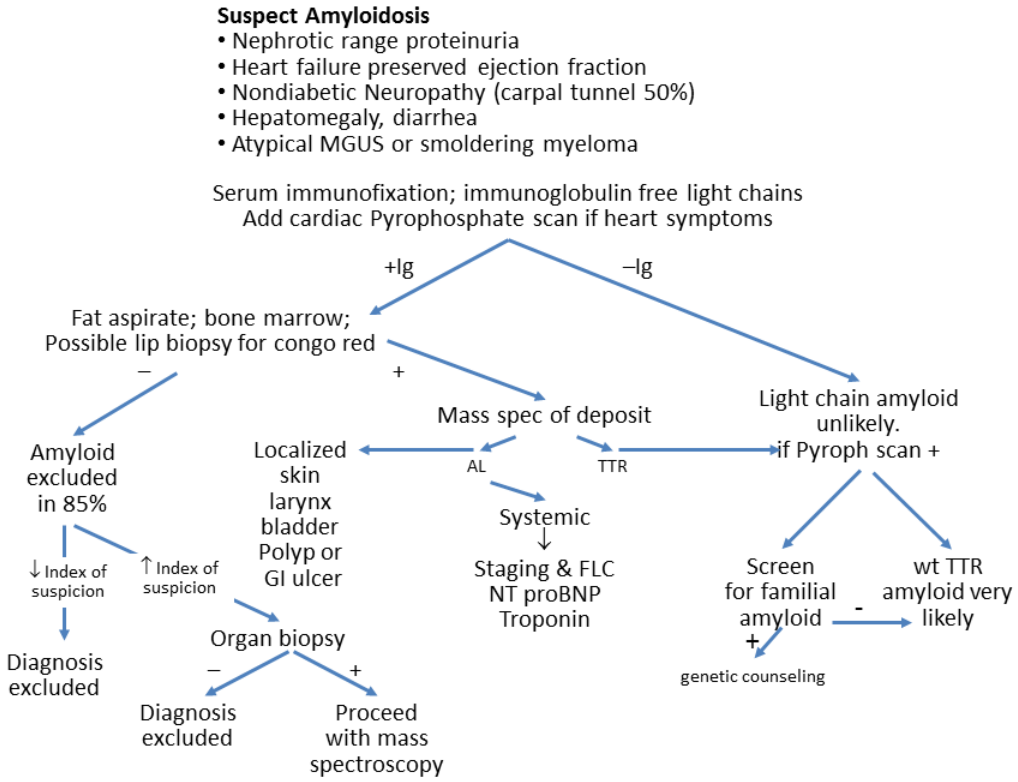
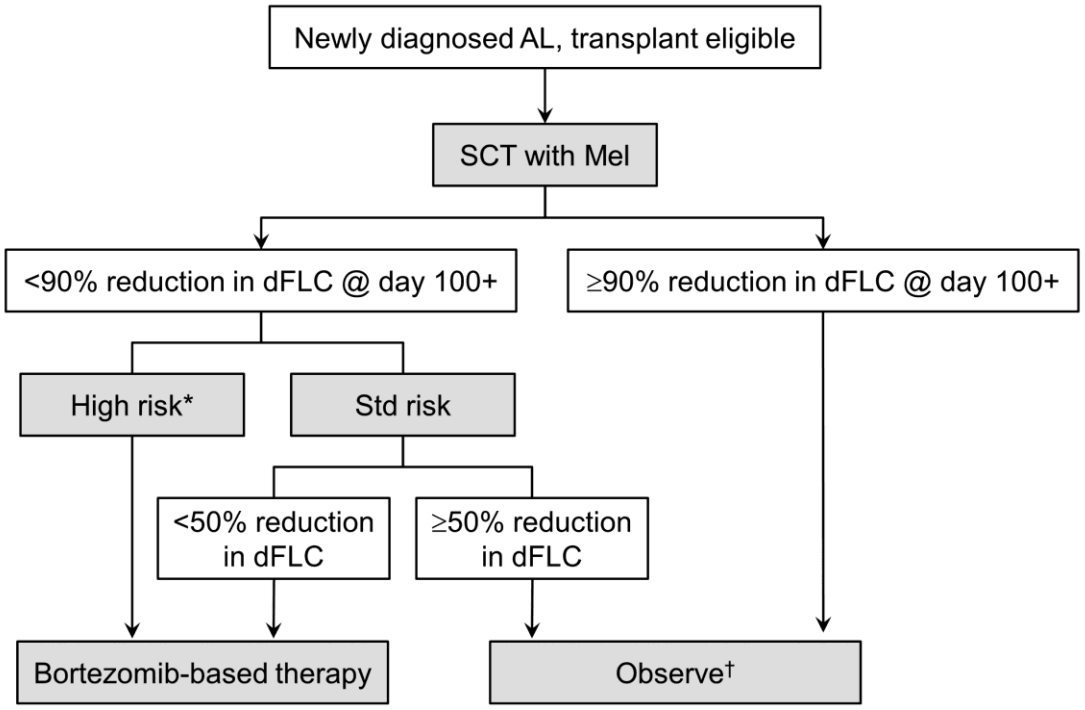


Figure 2. Algorithm for Evaluating Patients with Suspected Amyloidosis.



*High risk = Mayo Stage III (cTnT >0.035 μg/L and NT-proBNP >332 ng/L)
†Start alternate therapy if organ progression occurs at any time

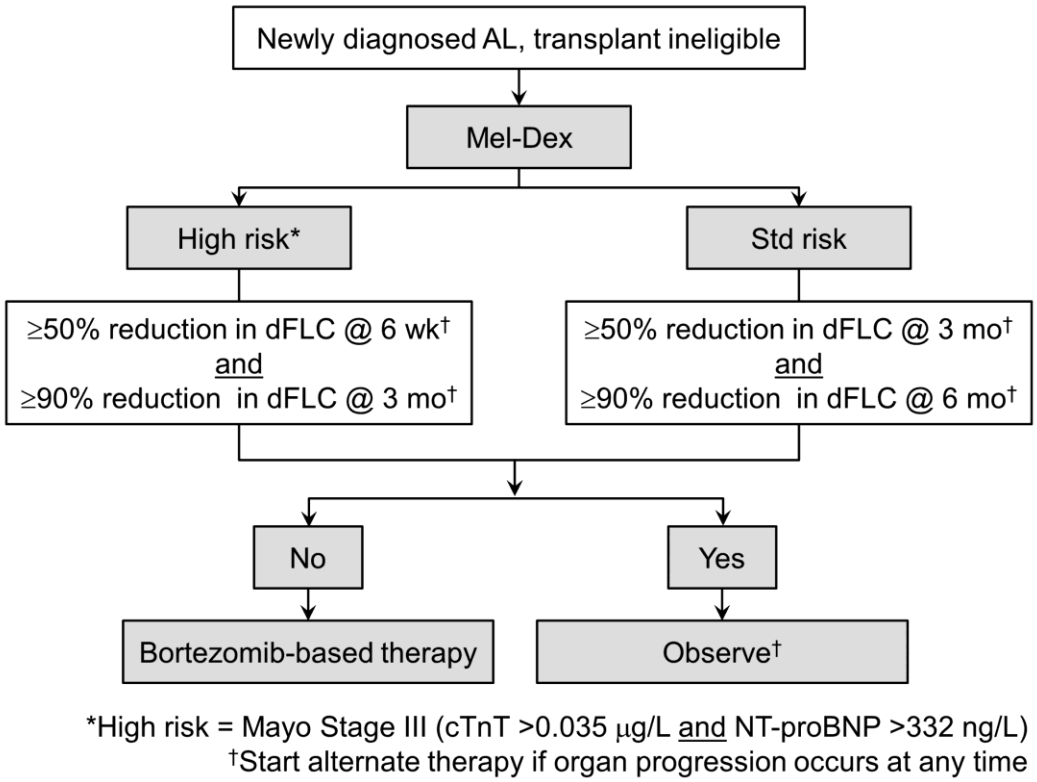


Figure 3. mSMART.org Guidelines for Treatment of Newly Diagnosed AL Amyloidosis (Off-Study). A, Transplant-eligible patients. B, Transplant-ineligible patients. AL amyloidosis indicates immunoglobulin light chain amyloidosis; cTnT, cardiac troponin T; Dex, dexamethasone; dFLC, difference between involved and uninvolved serum free light chain levels; Mel, melphalan; NT-proBNP, N-terminal pro–brain natriuretic peptide; SCT, stem cell transplant; Std, standard. Adapted from: http://msmart.org/amyloid.pdf.

Box. Required Diagnostic Evaluation After Amyloidosis is Established

- Pathologic confirmation that amyloid deposits are of immunoglobulin origin
- Immunoglobulin free light chain κ and λ testing
- Bone marrow biopsy
- Serum and urine immunofixation
- Echocardiography
- 24-hour urine total protein measurement
- Measurement of complete blood count, creatinine level, alkaline phosphatase level
- Measurement of troponin, brain natriuretic peptide, or N-terminal pro–brain natriuretic peptide levels
- Quantitative immunoglobulin measurement
- If TTR amyloidosis is suspected radionuclide imaging of the heart with Tc PYP or Tc DPD

Table 1. Agreement of Results of Fat Aspiration and Bone Marrow Biopsy in 378 Patients With a Diagnosis of AL Amyloidosis[a]

		Fat Aspiration		
		Positive	**Negative**	**Equivocal**
Bone Marrow Biopsy	Positive	202	59	10
	Negative	49	44	9
	Equivocal	3	2	0

[a] Results are both positive in 53.4% (202/378), one positive in 32.0% (121/378), and both negative or equivocal in 14.6% (55/378).

Table 2. Staging of Immunoglobulin Light Chain Amyloidosis

Score[a]	Median Survival, Mo
0	94.1
1	40.3
2	14.0
3	5.8

[a] Scores are calculated by assigning 1 point for each of the following: cardiac troponin T ≥0.025 ng/mL; N-terminal pro–brain natriuretic peptide ≥1,800 pg/mL; and difference between involved and uninvolved serum free light chain levels >180 mg/L.

Data from Kumar et al (46).

Table 3. Conventional Systemic Chemotherapy Options for AL Amyloidosis

Therapy	Comment
Melphalan-dexamethasone	Reported outcome dependent on proportion of cardiac patients
Cyclophosphamide-thalidomide-dexamethasone	All oral regimen thalidomide dose begins at 50 mg/d
Melphalan-lenalidomide-dexamethasone	Lenalidomide dose 10-15 mg, 21 of 28 days
Bortezomib-dexamethasone	Weekly dosing better tolerated, less neurotoxicity
Lenalidomide-cyclophosphamide-dexamethasone	Lenalidomide (15 mg), days 1-21; cyclophosphamide (300 mg/m^2; orally), weekly on days 1, 8, 15; every 28 days
Cyclophosphamide-bortezomib-dexamethasone	Response rates of 94% and 81% (90,91)
Bendamustine	Trial ongoing (NCT01222260)
Doxycycline	Trial ongoing (NCT01677286)
11-1F	Trial completed, multicenter study bing planned (NCT02245867)
89Zirconium-labelled GSK2398852	Biodistribution study heat TTR