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HOW TO MANAGE...

How to manage primary amyloidosis

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Immunoglobulin light chain amyloidosis is a protein deposition disorder where the precursor protein represents a monoclonal immunoglobulin light or heavy chain. Deposition in viscera results in restrictive cardiomyopathy, nephrotic range proteinuria, demyelinating peripheral neuropathy, hepatomegaly and malabsorption syndrome. Diagnosis requires biopsy with Congo red staining. Invasive biopsies are not required generally. It is essential that after a histologic diagnosis is obtained, the tissue is validated to have an immunoglobulin light chain composition so patients are spared unnecessary chemotherapy. The disease prognosis and patient monitoring are linked to serialized measurement of cardiac biomarkers and immunoglobulin-free light chains. Most patients require cytotoxic chemotherapy. For some patients, this therapy involves stem cell collection and myeloablative chemotherapy; for others, chemotherapy includes an alkylator and a corticosteroid; and for some, it involves addition of a novel agent in the form of an immunomodulatory drug or a proteasome inhibitor. Delays in diagnosis continue to be an obstacle to initiating effective therapy. Early mortality rates remain high. Effective chemotherapy can result in reversal of organ dysfunction and recovery. Reductions in light chain production translate to improved survival.
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Introduction

Immunoglobulin light chain amyloidosis (AL) is characterized by the production of clonal immunoglobulin light chains by a clonal population of plasma cells in the bone marrow. The amyloid deposits may consist of a light chain, a light chain fragment or a heavy chain fragment.[1] Misfolding of the light chain into the β-pleated sheet configuration results in the classic Congo red positivity,[2] showing apple-green birefringence under polarized light.

Making the diagnosis of AL

A patient can be referred to an oncologist for management of AL in one of three typical clinical scenarios.

Clinical scenario 1: the patient is referred with biopsy-proved AL

When a new patient is seen with a diagnosis of AL, the clinician should not assume that this patient immediately requires chemotherapy. AL often appears as a localized phenomenon with no risk of systemic visceral dysfunction, and these patients have a normal life expectancy. The first important question the oncologist must ask is, 'Is the patient's AL localized?'[3]

Localized AL is often first suspected on the basis of its location. Typical sites where AL is a localized, nonsystemic phenomenon are the skin,[4] brain, bladder,[5] ureter,[6] urethra and renal pelvis.[7] Other sites typically associated with localized AL include the conjunctiva,[8] larynx,[9] vocal cords and tracheobronchial tree.[10] Solitary pulmonary nodules typically represent localized nodular AL and do not require systemic therapy.[11] In all these clinical presentations, the patients have no evidence of a systemic monoclonal immunoglobulin disorder. In addition, immunofixation of the serum, immunofixation of the urine, immunoglobulin-free light chain analysis of the serum and analysis of bone marrow will fail to show evidence of a monoclonal plasma cell disorder.

If the patient has localized AL, systemic treatment is not indicated and the patient should be referred for localized therapy. Bladder AL is typically treated with laser resection[12] and, occasionally, installation of dimethyl sulfoxide.[13] Tracheobronchial AL is treated with bronchoscopic laser therapy[14] or external beam radiation to the deposits.[15] In these cases, recurrences are common. Life-long monitoring is necessary; chemotherapy is never indicated. A particularly important finding that may represent localized AL is amyloid detected on endoscopic biopsy[16] or colonoscopic biopsy.[17] This finding can be particularly confusing because these biopsies are often taken to validate the presence of light chain AL. A patient who has an incidental finding of AL on an endoscopic biopsy,[18] particularly when the biopsy was taken from the edge of an ulcer or in a polyp, should be considered to have localized disease until proved otherwise; care should be exercised before committing the patient to any form of systemic therapy.

If the patient referred with AL has systemic, nonlocalized disease, it is important to ensure that the AL is neither familial, senile nor secondary. Some patients have nonimmunoglobulin forms of systemic AL, although it is uncommon. At autopsy—beyond age 90 years—nearly 25% of patients have senile amyloid deposits in the heart[19] that may contribute to cardiac dysfunction and are not amenable to chemotherapy. Sporadically, cardiac AL develops on an inherited basis without evidence of a family history.[20] The consideration that AL may be familial is particularly important in the African-American population, where the prevalence of mutant transthyretin VAL122ILE approaches 3%[21] and an accurate family history of late-onset cardiomyopathy may be difficult to obtain.

Occasionally, patients are seen with secondary AL because of a well-defined rheumatic disorder, such as spondyloarthropathy or long-standing inflammatory, symmetrical polyarthritis, but often, less well-defined connective tissue disorders with sustained systemic inflammation can result in the development of secondary AL.[22] These patients do not have evidence of a monoclonal gammopathy unless an incidental monoclonal gammopathy of uncertain significance is present.

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Verification of the type of amyloid in the tissue biopsy specimen is critical. When the result of immunohistochemistry is definitive, it is an acceptable alternative for classifying the AL.[23] However, the gold standard is mass spectroscopic analysis[24] of the tissue and direct sequencing to identify the amyloid protein.[25] This analysis is now standard for all pathologic specimens that are positive on Congo red stain seen at Mayo Clinic. The distinction between immunoglobulin and nonimmunoglobulin AL is important because nonimmunoglobulin AL not only does not benefit from chemotherapy, but also new trials are under way with drugs, including both eprodisate, for slowing the decline of renal function in secondary AL,[26] and tafamidis,[27] which has potential utility in the management of senile and familial AL. In addition, studies of experimental preclinical therapies are exploring transthyretin interfering RNAs.[28] For selected patients, liver transplantation for transthyretin inherited AL is an appropriate consideration.[29]

If systemic AL is confirmed, the patient needs to be evaluated as outlined in Table 1. Tests of immunoglobulin-free light chain levels and a bone marrow sample are indicated, as is a serum troponin test, a B-natriuretic peptide test and echocardiography. A summary of how to treat patients in scenario 1, referred with biopsy-proved AL, is given in Table 2.

Table 1 Suggested diagnostic evaluation of suspected light chain amyloidosis

- Confirmation that amyloid deposits are of light chain origin
- Serum and urine electrophoresis and immunofixation and immunoglobulin free light chain
- Quantitative immunoglobulin test
- Marrow aspirate biopsy and analysis with Congo red stain
- Complete blood cell count; alkaline phosphatase and creatinine tests
- Echocardiography
- Troponin test
- NT-proBNP test
- Bilirubin test, prothrombin time and factor X level

Abbreviation: NT-proBNP, N terminal of prohormone brain natriuretic peptide type B.

Table 2 Scenario 1: patient referred to hematologist with biopsy-proved amyloidosis

1. Could amyloidosis be localized?
- Skin
- Brain
- Bladder
- Larynx, pulmonary nodule
- Endoscopic biopsy only

2. Screening immunofixation of serum, urine, free light chain
If amyloid is visceral (that is, renal, cardiac, hepatic or nervous system):
Could amyloidosis be nonimmunoglobulin type—secondary, familial or senile?

Mass spectroscopic analysis of amyloid deposit to confirm type
If non-light chain derived, referral for therapy trials, including eprodisate and tafamidis, and possible liver transplantation

If light chain-derived AL amyloid confirmed, perform serum and urine immunofixation, free light chain, marrow, troponin, NT-proBNP, echocardiography

Abbreviation: NT-proBNP, N terminal of prohormone brain natriuretic peptide type B.

Scenario 2: the patient has a known plasma cell dyscrasia. Should the patient be assessed for AL?

When a patient with a known plasma cell proliferative disorder has bone marrow plasma cells ranging from 5 to 20% without typical features of multiple myeloma, such as cases of lytic bone disease or high urinary light chain levels, the clinician should ask whether the patient has any of the following signs and symptoms:

- Signs of 'atypical' multiple myeloma with substantial fatigue disproportionate to the level of anemia (considering amyloid heart disease).
- A peripheral neuropathy. Although this finding has the potential to be associated with multiple myeloma, the possibility of amyloid neuropathy must not be overlooked, particularly when the patient has a λ monoclonal protein.
- Heavy albuminuria. Electrophoresis of the urine of a patient with multiple myeloma usually shows only small amounts of albumin, with substantial excretion of urinary monoclonal light chains. By comparison, a patient with amyloid has predominant albuminuria and the light chain fraction is relatively modest.
- The patient has unexplained edema, which could be due to hypoalbuminemia, to urinary protein loss or to restrictive cardiomyopathy[30] and high filling pressures on the right side of the heart.

If the clinician is caring for a patient with myeloma with any of these unusual features, the bone marrow that showed the plasma cell dyscrasia should be stained for amyloid deposits, and a subcutaneous fat aspirate should be obtained and evaluated for amyloid. Table 3 lists the treatment steps for a patient with a known plasma cell dyscrasia but also with atypical features that do not suggest classic multiple myeloma. Routine Congo red staining of the bone marrow of a patient with typical multiple myeloma is not indicated.[31]

Scenario 3: the patient is sent by a subspecialist with the request, 'please rule out AL'

As AL occurs in only eight persons per 1 million per year,[32] the clinician should be familiar with the presenting syndromes that indicate whether an evaluation is appropriate. For example, chronic pain is not consistent with AL. Enlargement of the tongue and periorbital purpura, as well as periarticular infiltration (shoulder pad sign), are well-recognized features of AL. Yet, these signs occur in only 15% of patients.[33] Physical signs are not a sensitive method of excluding the diagnosis. The oncologist should look for any of the following syndromes: (1) nephrotic range proteinuria, (2) fatigue or dyspnea that could potentially be due to an unrecognized cardiomyopathy, (3) sensorimotor peripheral neuropathy and (4) hepatomegaly without imaging defects.[34] The most subtle among these four syndromes is cardiomyopathy. As the cardiomyopathy is restrictive, these patients have no evidence of coronary artery disease and lack cardiomegaly on chest radiography.[35]

Table 3 Scenario 2: patient has a known plasma cell dyscrasia

Should patient be assessed for amyloidosis?
- 'Atypical' myeloma with fatigue disproportionate to anemia
- Peripheral neuropathy
- Heavy proteinuria
- Severe edema

Stain marrow specimen for amyloid and perform subcutaneous fat aspiration

Table 4 Scenario 3: patient referred with the request 'please rule out amyloidosis'

Does the patient have any of the following conditions?

- Nephrotic-range proteinuria
- Fatigue or dyspnea that could be due to cardiomyopathy
- Sensorimotor peripheral neuropathy
- Hepatomegaly with no imaging abnormalities

If no, why was amyloidosis suspected?

If yes, electrophoresis and immunofixation of serum, urine and free light chain
If positive, biopsy fat or marrow, or biopsy organ if necessary
If negative, light chain amyloidosis excluded, inherited disorder not excluded

The thickening of the ventricle wall may be misinterpreted as hypertrophy. An electrocardiogram may show a pseudoinfarction pattern that may be interpreted as silent ischemic heart disease.

If the patient has none of the four syndromes, the clinician should question why AL was suspected. If the symptoms are consistent, immunofixation and electrophoresis of the serum, urine, and free light chains should be done. If any of these studies are positive, then biopsy of the subcutaneous fat and bone marrow and, if necessary, an organ biopsy should be performed to confirm AL. However, if the light chain studies are negative, the likelihood that the patient has light chain AL is small; unless there is a clear history of an inherited or inflammatory disorder, further diagnostic testing is not indicated. Table 4 lists the steps to undertake for a patient referred with a 'rule out AL' request. Table 1 lists the recommended diagnostic evaluation for patients who have histologic proof of AL.

Prognosis

Prognosis in AL is intimately linked to the severity of the cardiac involvement. One reason that the outcomes in AL continue to be poor is late diagnosis of amyloid cardiomyopathy. The cause of death in >70% of patients with AL is progressive cardiac failure or sudden death,[36] which usually represents asystolic arrest related to cardiac hypoperfusion or sudden arrhythmia.

The ability to assess amyloid cardiomyopathy has been refined over time. Cardiac failure was defined historically by clinical symptoms and the chest radiograph. The introduction of echocardiography allowed recognition of wall and valvular thickening, the granular sparkling appearance,[37] and, with the introduction of Doppler,[38] relaxation abnormalities leading to a rapid rise in filling pressures during diastole. Ten years ago, the first studies were reported on the use of magnetic resonance imaging to demonstrate wall thickening and the specificity of subendocardial enhancement after gadolinium infusion.[39] None of these techniques are quantitative, and the introduction of cardiac biomarkers—both troponin and the N terminal of prohormone brain natriuretic peptide type B (NT-proBNP)[40]—has been found to be useful in defining prognosis and estimating survival, as well as providing a method to serially determine whether myocardial function is improving, stable, or progressing after therapy. A high troponin T level should serve as an exclusionary criterion for undertaking stem cell transplantation.[41] Other important prognostic factors include the percentage of bone marrow plasma cells before therapy[42] and the level of immunoglobulin-free light chains[43] at diagnosis, as well as the serum uric acid level.[44]

Assessing response

In multiple myeloma, outcome is determined by reductions in the tumor mass, with the M protein acting as a surrogate for bone marrow plasma cell burden. The same cannot be said for AL.

The median number of plasma cells in the bone marrow in patients with AL is approximately 4%, and the tumor mass does not accurately predict outcomes.[45] Death is the ultimate result of the inexorable deposition of immunoglobulin light chains as amyloid deposits, leading to progressive visceral infiltration and organ dysfunction. Reducing monoclonal immunoglobulin light chain production is critically important to ensuring a good outcome. Changes in the serum-free light chain, rather than the intact monoclonal immunoglobulin, appear to be the key end point for evaluating therapy in primary AL.[46]

Response criteria are under development by a consensus panel for AL treatment. The proposed new criteria require a partial response, defined as a decrease in >50% in the difference between involved and uninvolved immunoglobulin light chain. A very good partial response would be defined as a difference in the involved and uninvolved immunoglobulin-free light chain of <4 mg/dl, and a complete response would be negative immunofixation serum and urine and a normal-free light chain ratio.[47] With respect to cardiac organ response and progression, NT-proBNP criteria were defined as a change of 30% and at least 300 ng/l, using a minimum NT-proBNP of 650 ng/l to be considered evaluable, for response and progression reporting. Figure 1 shows the survival of patients using the four categories of response as proposed.

Therapy

Pending the development of strategies that destabilize the amyloid fibril, either by preventing the binding of serum amyloid P component or by using agents that interfere with the misfolding of a soluble light chain to an amyloid confirmation, the treatment involves cytotoxic chemotherapy designed to disrupt the production of the immunoglobulin light chain precursor protein. Mayo Clinic investigators have reported recently on two cohorts of patients seen before and after 1 September 2006, and have recognized the steady improvement in 4-year overall survival from 21 to 42%. However, early mortality rate continues to be 44% at 1 year, and this statistic has remained unchanged for 30 years.[48] Some of this

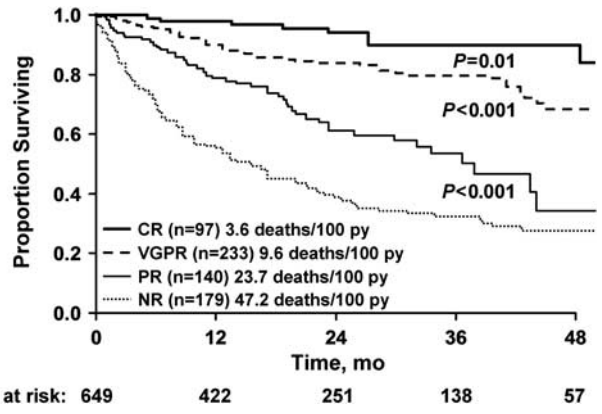

Figure 1 Survival by the new staging system in immunoglobulin light chain amyloidosis. CR, complete response; NR, no response; PR, partial response; py, patient-year; VGPR, very good partial response (adapted from Palladini *et al.*[47] Used with permission).

improvement in survival may reflect lead time bias because of earlier diagnosis and improved recognition. The predictors of early death were troponin, NT-proBNP and uric acid; 1-year death ranged from a low of 19% with none of these factors to 80% with all of the factors. Despite the possibility of lead time bias, improvement in therapy—the use of both stem cell transplantation and novel agents—has had an important role in enhancing the outcomes for this patient population. Alkylator-based chemotherapy for AL was first used 39 years ago in a case report.[49] The use of melphalan and prednisone was reported subsequently in three studies to show response rates (measured before the introduction of the light chain assay) of approximately 20% with survival benefit compared with colchicine, a treatment that was introduced in the 1970s and subsequently abandoned as ineffective.[50–52] The advantage of chemotherapy based on melphalan and prednisone was that virtually any patient was eligible to receive the therapy, and we consider a trial of this well-tolerated treatment an option for virtually all patients without regard to the extent of cardiac involvement or performance status.

Alone, corticosteroids have activity in the treatment of AL. Three studies on the use of dexamethasone have shown objective responses and regression of renal AL, although little impact was seen in patients with advanced cardiac involvement.[53–55]

Stem cell transplantation for AL was introduced 15 years ago. This technique has been shown to produce high responses and substantial survival prolongation. However, no >20% of patients are eligible for the technique because of advanced age, renal insufficiency, advanced cardiac failure or multiorgan involvement. Table 5 gives Mayo Clinic's criteria for stem cell transplantation eligibility. Stem cell transplantation has limited application because of a high treatment-related mortality rate if patients are not carefully selected. However, Mayo Clinic investigators have shown declining mortality rates in patients who have received a transplant. After 2006, a day-100 all-cause mortality rate of <7% was seen. From 1 January 2010, through 1 April 2011, no treatment-related deaths (any cause before day 100) at Mayo Clinic in Rochester, MN, USA, occurred in the 46 patients with AL who received a transplant.[56] It is our hope that this survival relates to the implementation of stricter selection criteria using troponin, assessment of cardiac reserve and severity of noncardiac organ involvement.

An important predictor of stem cell transplantation outcome is the selection of patients. Patients with high levels of troponin should not be considered eligible for transplantation.[41] One series recently showed a complete response rate of 49%, higher than that reported with melphalan and dexamethasone therapy.[57] However, one prospective randomized study[58] and one published meta-analysis[59] do not demonstrate a survival advantage for stem cell transplantation. Yet, these studies included patients who should not have been selected for transplantation, and the resultant high treatment-related mortality rate resulted in no difference between groups.[60]

Mayo Clinic investigators recently reported results of 430 patients with AL.[61] The patients with a complete response have not attained median survival yet. For those with a partial response, median survival was 107 months; for those with no response, it was 32 months. In this study group, cardiac stage was the sole predictor of survival. A quarter of the patients had >13% plasma cells in the bone marrow. The overwhelming majority were diagnosed through either bone marrow or fat aspiration (86%), showing that biopsy of liver, heart and kidney is generally unnecessary when the diagnosis is suspected. Neutrophil engraftment occurred at a median of 13.5 days and platelet engraftment at 17.5 days. The median length of hospital stay was 8 days, with 19% of patients completing their stem cell transplantation as an outpatient. Responses were seen in all organ systems, including cardiac, renal and hepatic. The day + 100 all-cause mortality rate was 10.1% going back to the beginning of the program. Organ responses were seen in 47% of patients overall. We continue to believe that stem cell transplantation is the preferred technique for patients in whom the mortality risk is thought to be low, at <10%.

Table 5 Exclusion criteria for high-dose chemotherapy in AL

Physiologic age >70 years
Serum creatinine >175 mcmol/l (>2.0 mg/dl)
Troponin T⩾0.06 mg/l
Orthostatic syncope
Advanced cardiac involvement
ECOG PS >2
NYHA class III or IV
Large pleural effusions
Oxygen therapy dependency
Multiorgan involvement
Biochemical-only multiorgan involvement with soft tissue amyloid, or biopsy without symptoms excluded from multiorgan involvement

Abbreviations: AL, immunoglobulin light chain amyloidosis; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NYHA, New York Heart Association.

Chemotherapy treatment for AL in 2011

As the majority of patients with AL are not eligible for stem cell transplantation, controversy exists as to the optimal therapy. With the knowledge that melphalan and prednisone, as well as single-agent dexamethasone, were effective in treatment of AL, investigators combined melphalan with dexamethasone in the treatment. In the largest reported series, patients ineligible for stem cell transplantation received cyclic melphalan and dexamethasone therapy, with an actuarial survival of 50% at 6 years and a progression-free survival of 40%.[62,63] However, other studies have not shown as good a result, presumably because they had a higher proportion of patients with cardiomyopathy.[64,65] In a study of 48 evaluable patients with AL who survived to return for a follow-up visit in Boston, 13% achieved a complete response and 25% a partial hematologic response. Median survival for 70 evaluable patients was not reached with a median follow-up of 17 months. Melphalan and dexamethasone can lead to hematologic responses and improvement in survival.[66]

Interpreting the results of clinical trials of patients with AL requires knowledge of cardiac staging, to ensure the comparability of the patient population. High proportions of enrolled patients with advanced cardiac AL will result in poor study outcomes. A low prevalence of cardiac AL will likely result in better reported response rates and survival. This impact of patient selection on the outcome must be kept in mind when interpreting published results.[67]

In the opinion of Mayo Clinic physicians who specialize in AL, melphalan and dexamethasone is still considered the standard for nonstudy, nontransplantation patients because of its low toxicity profile, its oral availability, and the ability to produce hematologic responses in patients with advanced AL. Subsequent studies have been designed to build on the melphalan–dexamethasone treatment backbone.

Novel agents in the treatment of AL

Thalidomide. Thalidomide is used in AL treatment, but as a single agent, it shows low activity. In the first published case series of its use in patients with AL, no organ responses were seen.[68] In a subsequent study, hematologic responses were reported in 48%—including 19% with complete response—but the agent was poorly tolerated.[69] Melphalan–thalidomide–dexamethasone combination therapy has been used for 22 patients, resulting in eight hematologic responses (36%).[70]

The best reported results have been with the combination of thalidomide, cyclophosphamide and dexamethasone.[71] The hematologic response rate appears to be 74%, with a complete response in 21% and a median overall survival of 41 months. The treatment-related mortality rate was 3%. When thalidomide is used, the initial dose should probably not exceed 50 mg per day. In a review of 428 patients with AL, 155 patients (36%) received cyclophosphamide–thalidomide–dexamethasone combination treatment.[72] A hematologic complete response and partial response were seen in 22% and 41%, respectively, with a median reduction of 72% in the difference between involved free light chain and uninvolved free light chain. There was no significant difference in the overall survival of patients treated with cyclophosphamide–thalidomide–dexamethasone therapy or melphalan–dexamethasone therapy.

Lenalidomide. Lenalidomide has been combined with dexamethasone in the treatment of AL. Toxicities were substantial and included cramps, fatigue, rash and cytopenias. In the first published study of lenalidomide–dexamethasone treatment of AL, hematologic response rate was 41% and median overall survival was 31 months.[73] In an update, progression-free survival of patients with complete response was 49.8 months.[74] In a second study, 41% of patients with renal amyloid had a reduction in urinary protein, but the response duration and overall survival were not reported.[75] In that study, high-risk patients were less likely to respond to lenalidomide.

Lenalidomide also has been combined with melphalan and dexamethasone.[76] The maximum tolerated dose of lenalidomide is 15 mg. This three-drug oral combination produced hematologic responses in 58% and complete responses in 42%. The 2-year event-free survival and the overall survival were 54% and 81%, respectively. In addition, lenalidomide was combined with cyclophosphamide and dexamethasone in the treatment of 35 patients.[77] Hematologic response rate was 60%. In those patients receiving at least four treatment cycles, the response rate was 87%. Median overall survival was 16.1 months.

A randomized study of cyclophosphamide–thalidomide–dexamethasone treatment compared with melphalan–dexamethasone treatment suggested a greater complete response rate with the three-drug regimen, albeit with greater toxicity.[78] One cautionary note when using lenalidomide or thalidomide in patients with AL is that the NT-proBNP level appears to increase after the initiation of therapy. Recognition of potential immunomodulatory drug-induced cardiac toxicity is important when these agents are used. High levels of NT-proBNP are predictive of an inability to tolerate immunomodulatory agents for AL.[79,80]

Pomalidomide. Pomalidomide, a derivative of thalidomide with structural similarity to thalidomide and lenalidomide, was given to 29 evaluable patients in one study.[81] All patients received treatment previously and 13 of the patients received a prior autologous stem cell transplantation. Previously, an immunomodulatory agent was given to 15 patients and bortezomib to 12. Twenty-nine patients evaluable for hematologic response were seen. The overall response rate was 11 (38%) of the 29 patients. Combined treatment with pomalidomide and dexamethasone is promising.[81] One-year survival and progression-free survival was 77% and 56%, respectively. Pomalidomide was considered effective and safe for patients, including those in whom prior lenalidomide or thalidomide therapy had failed.

Bortezomib. Of evaluable patients in the first reported study of bortezomib in AL treatment, 80% had a hematologic response.[82] Among 18 patients, the hematologic response was 77%, with a complete response of 16%. A phase 1 dose-escalation study of bortezomib given either twice weekly on days 1, 4, 8 and 11 every 21 days or on days 1, 8, 15 and 22 every 35 days reported hematologic responses in 50% of patients.[83] The weekly regimen was associated with less neurotoxicity. The 1-year hematologic progression-free rate was 72.2% and 74.6% and the 1-year survival rate was 93.8% and 84%, respectively, for the twice-weekly and once-weekly doses. Among 70 patients, there were 29% renal responses and 13% cardiac responses. Discontinuation and dose reduction because of the toxicity were higher with the twice-weekly dose than the once-weekly dose. Both dose schedules represent active, well-tolerated regimens in relapsed AL.[84]

The combination of bortezomib and dexamethasone has been used to render a patient eligible for stem cell transplantation after organ improvement was seen with bortezomib treatment. Bortezomib was also used successfully after relapse following stem cell transplantation.[85] Twenty-six patients with AL received bortezomib and dexamethasone, and 31% achieved a complete response and 12% an organ response.[86] A multicenter study of 94 patients receiving bortezomib and dexamethasone showed hematologic responses in 71%, of which 25% were complete responses.[87] Cardiac response was seen in 29% of patients. NT-proBNP analysis predicted survival. In a study of bortezomib–dexamethasone therapy in 26 patients with AL, the overall response rate was 54% and the complete response rate was 31%.[86] Median time to response was 7.5 weeks, but the median progression-free and overall survival was 5.0 and 18.7 months, respectively, suggesting short response durability with bortezomib combined with dexamethasone. No grade 3/4 neuropathy was seen. Recommended treatment for newly diagnosed AL and relapsed AL is given in Figures 2 and 3. Reported regimens for the nontransplantation treatment of AL are given in Table 6.

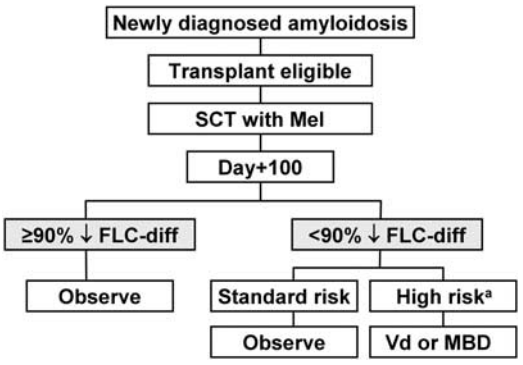

Figure 2 Approach to treatment of transplant-eligible patients with AL. [a]High risk indicates stage III. FLC-diff, the difference between involved (amyloidogenic) free light chain and uninvolved free light chain; MBD, melphalan–bortezomib–dexamethasone; SCT, stem cell transplantation; Vd, bortezomib ± dexamethasone (adapted from http://msmart.org/amyloid.pdf).

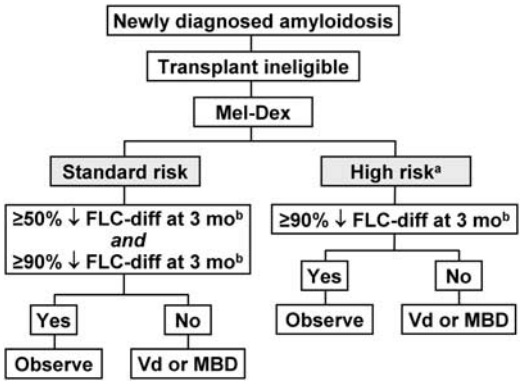

Figure 3 Approach to treatment of transplant-ineligible patients with AL. [a]High risk indicates stage III. Consider upfront Vd or MBD in younger patients. [b]Start alternative therapy if organ progression has occurred at this point. FLC-diff, the difference between involved (amyloidogenic) free light chain and uninvolved free light chain; MBD, melphalan–bortezomib–dexamethasone; Mel-Dex, melphalan–dexamethasone; Vd, bortezomib ± dexamethasone (adapted from http://msmart.org/amyloid.pdf).

Table 6 Nontransplantation treatment options for amyloidosis

Melphalan–dexamethasone
Bortezomib ± dexamethasone
Melphalan–dexamethasone–lenalidomide
Cyclophosphamide–thalidomide–dexamethasone
Cyclophosphamide–bortezomib–dexamethasone
Melphalan–prednisone–bortezomib

Conclusion

Chemotherapy is capable of producing a hematologic response, as well as improvement in organ function of patients with AL. Hematologic response has been shown to translate into improved survival. When a patient is seen with a compatible syndrome, studies to exclude localized, inherited and secondary AL should be performed. Mass spectroscopy is the gold standard for confirming the type of AL. After the diagnosis is confirmed, the prognosis should be assessed with use of echocardiography and testing for cardiac biomarkers. Some patients will be appropriate candidates for stem cell transplantation. For others, melphalan–dexamethasone treatment, with the possible addition of an immunomodulatory drug or a proteasome inhibitor, should be considered.

Conflict of interest

The author receives honoraria from Celgene and Millennium.

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