Amyloidosis

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Opinion statement

Amyloidosis is a disease in which abnormal proteins form fibrillar tissue deposits that can compromise key viscera and lead to early death. In order to treat amyloidosis, the type of abnormal protein must be identified. The most common type is monoclonal immunoglobulin light chain or AL amyloidosis; the other important type is hereditary, caused by variant forms of transthyretin and other proteins, whereas amyloid associated with chronic inflammation ("secondary") is rare in the developed world. AL can be misdiagnosed if a monoclonal gammopathy and a hereditary variant are present in the same patient. The aim of therapy in systemic AL amyloidosis is to reduce the amyloid-forming monoclonal light chain, measured with the serum free light chain assay, by suppressing the underlying plasma cell dyscrasia, while using supportive measures to sustain organ function. Amyloid deposits can be resorbed and organ function restored if the amyloid-forming precursor light chain is eliminated. The most effective treatment for systemic AL amyloidosis is risk-adapted melphalan with peripheral blood stem cell transplant (SCT). The hematologic response rate is 75% at 12 months when adjuvant therapy with thalidomide and dexamethasone is used post-SCT. Patients can achieve long-term durable remissions with organ recovery. Drugs effective in multiple myeloma are usually helpful in AL amyloidosis if tolerated. The use of novel antibody-based approaches for imaging amyloid and possibly for accelerating removal of deposits is under active investigation.

Introduction

Amyloidosis is a disease of protein misfolding [1–3,4•]. Systemic AL amyloidosis is of importance to hematologists and oncologists because clonal plasma cells secrete the monoclonal light chain proteins that form fibrils [5,6••]. Stopping the production of the fibril-precursor protein is the central tenet of therapy [7]. Features of and approaches to AL amyloidosis are depicted in Figure 1A-C.

SYSTEMIC AL AMYLOIDOSIS

Systemic AL amyloidosis is a rare disorder with an incidence estimated to be 8 per million person-years. The median age at diagnosis is 63 years, and only 10% of patients are younger than 50 years. The median survival of patients seen within 1 month of diagnosis is approximately 1 year without treatment. Patients with congestive heart failure have a median survival of 4 months. In the pre–stem cell transplant (SCT) era, less than 5% of all AL amyloidosis patients survived 10 years or more from diagnosis [8,9]

A third of patients present with significant albuminuria, often with few symptoms associated with other organs of involvement, whereas another third present with symptoms of cardiac involvement including dyspnea on exertion and findings of diastolic dysfunction and left ventricular hypertrophy without a history of hypertension. Liver and gastrointestinal involvement are prominent at presentation in 25% of patients, with complaints that can include right upper quadrant discomfort, abdominal distension, weight loss, early satiety, and gastrointestinal bleeding. Peripheral neuropathy occurs in approximately 20% of patients at presentation and can cause sensorimotor symptoms that begin in the lower extremities and autonomic symptoms that can include orthostasis, diarrhea or constipation, and erectile dysfunction.

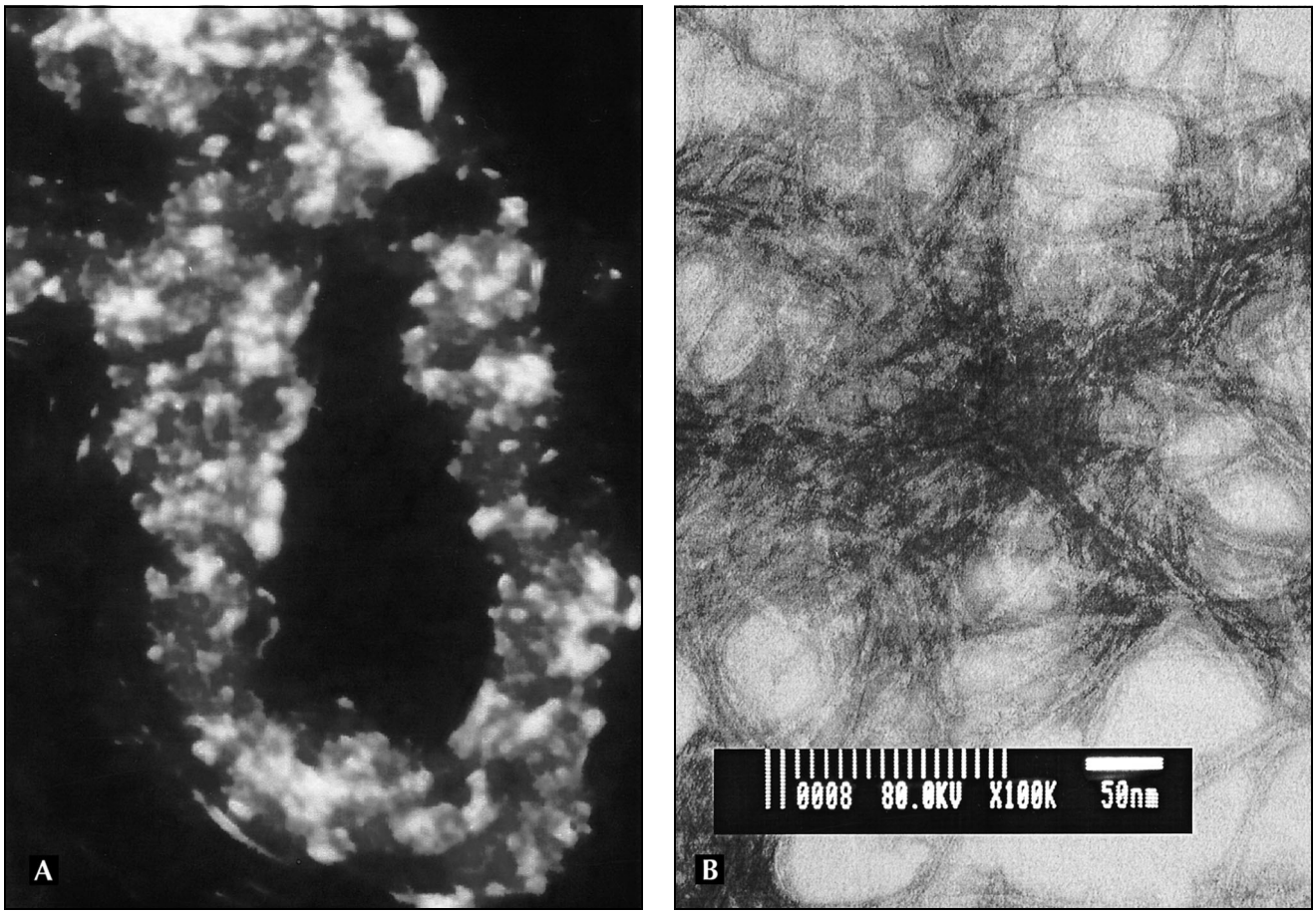


Figure 1. A, Congo red–stained tissue section is viewed in polarized light showing the pathognomonic apple-green dichroism of amyloid. (*Courtesy of* Bradly Clark, MD; Olympus digital camera 100 × magnification.) The type of amyloid cannot be reliably identified by tissue staining, and in a small number of cases additional genetic and protein-based studies are required [16,17,51,52]. **B**, Amyloid fibrils can be extracted and visualized by scanning electron microscopy. The fibrils have a characteristic appearance—they are linear, nonbranching, and 8–10 nm in diameter. (*Courtesy of* Limin Wang, PhD; Memorial Sloan-Kettering Core Electron Microscopy Laboratory.) Electron microscopy is clinically useful in patients who require biopsy of involved organs such as the kidneys or heart if prior surrogate-site biopsy results were negative or equivocal.

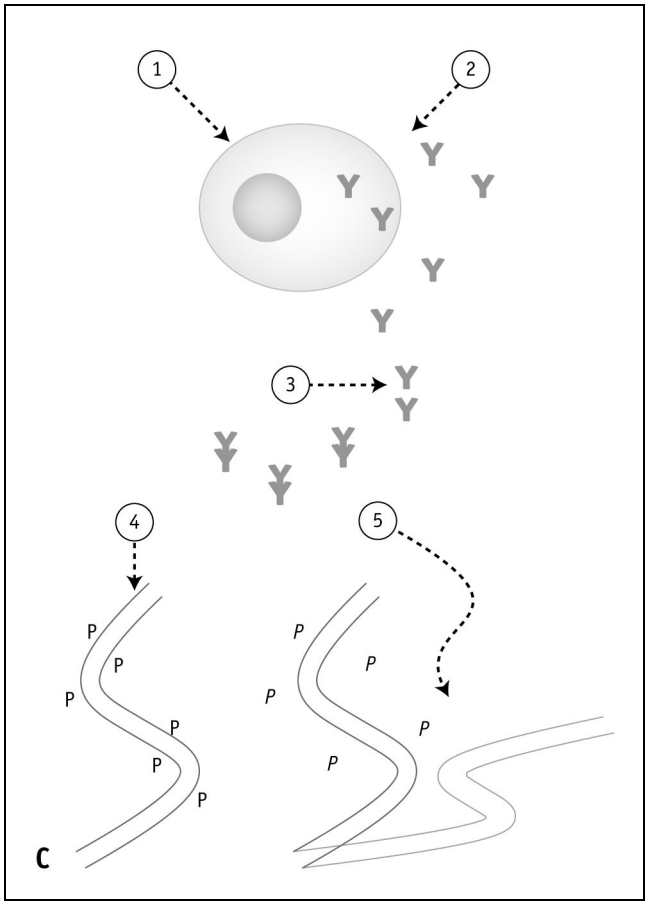
Diagnosis requires biopsy, of a surrogate site (abdominal fat, gingival, or rectum) or of an involved organ. The surrogate biopsy sites are rich in blood vessels and positive for amyloid in more than 80% of cases [10]. Staining the biopsy with Congo red is necessary to appreciate the pathognomonic red to apple-green dichroism that occurs when Congo red–stained amyloid is viewed in normal and then polarized light (Fig. 1A).

Free monoclonal light chains circulate in the blood of more than 95% of patients with AL amyloidosis, whereas plasma cells compromise less than 10% of marrow cells in nearly two thirds of patients [11–13]. Lambda clones dominate kappa clones in amyloidosis by a 3:1 ratio, unlike the 2:3 ratio in myeloma. The serum free light chain (FLC) assay, serum and urine immunofixation studies, and immunohistochemical staining of marrow biopsies for CD138, kappa, and lambda, and for amyloid with Congo red staining, are necessary aspects of the evaluation in order to characterize the plasma cell disease. (Rarely AL amyloidosis can be associated with lymphoplasmacytic disorders, and the evaluation would include radiographic and immunohistochemical studies appropriate for lymphoma [14].)

Severe anemia, lytic bone lesions, hypercalcemia, and hyperviscosity are not features of AL amyloidosis. Coagulation abnormalities can occur in patients with hepatosplenic AL amyloidosis because of deficiencies of factor X and dysfibrinogenemias; visceral rupture also occurs in a small fraction of patients with hepatosplenic AL [15]. The plasma cell disease that causes AL then is usually similar to a monoclonal gammopathy or a Durie-Salmon stage I myeloma. However, the relentless advance to end-stage organ dysfunction and death dominates the natural history of the disease.

DISTINGUISHING AL AMYLOIDOSIS FROM HEREDITARY VARIANTS OF AMYLOIDOSIS

Concerns about whether amyloid is AL or another type are warranted because myelotoxic chemotherapies have



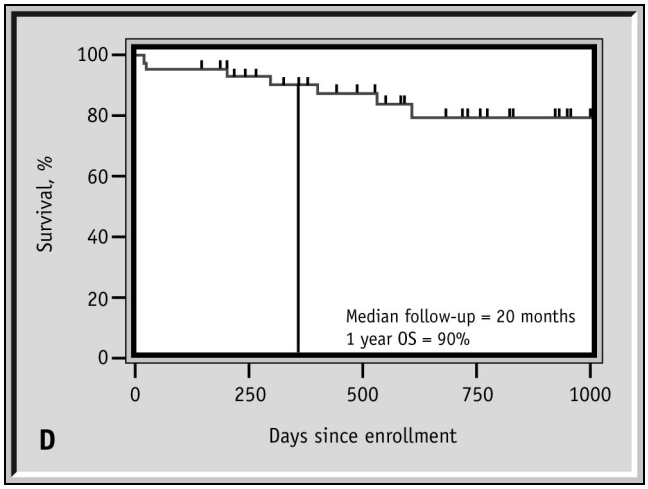


Figure 1. (*continued*) C, Treatment of AL amyloidosis could theoretically involve interruption of different steps in the pathophysiologic process as shown in this sketch. Step 1 is the "factory"—the clonal plasma cells secreting immunoglobulin light chains (Y). Therapy conventionally involves this aspect of the disease seeking to cytoreduce the clonal plasma cell population; therefore, treatments of use in myeloma traditionally have been pirated for use in AL amyloidosis [53]. Steps 2, 3, 4, and 5 represent the processes of light chain misfolding, aggregation, fibril assembly, and fibril dissolution. Immunotherapy with antibodies directed against epitopes in AL amyloidosis targets step 5 [47]. **D**, Stem cell transplantation (SCT) for this disease is a platform upon which additional adjuvant therapies can be added for those not achieving complete responses. Failure to achieve a complete response is associated with shorter 5-year survival, highlighting the relentless nature of the disease [36••]. This survival curve depicts survival in a clinical trial in which patients underwent risk-adapted melphalan SCT and then received adjuvant thalidomide and dexamethasone for 9 months if they did not achieve a complete response with SCT [42]. Note that there is no abrupt decrease in survival in the first 100 days; this approach had an overall treatment-related mortality of less than 5%. OS—overall survival.

no place in the treatment of hereditary or secondary amyloidosis. Investigators in the United Kingdom reported that of 350 patients thought to have AL, 10% had hereditary variants instead, including patients who had understandably failed SCT. They noted that hereditary variants have variable penetrance, making family history an ineffective screen, and that the immunohistochemical staining techniques used to type amyloid as derived from immunoglobulin light chains were unreliable [16].

Misdiagnosis of AL can lead to inappropriate use of chemotherapy and failure to diagnose a hereditary disease. Over a 3-year period at Memorial Sloan-Kettering Cancer Center (New York, NY), we sought to determine how often both possible sources of amyloidosis occurred in the same patient [17]. One hundred and seventy-eight consecutive patients were evaluated for amyloidosis and the diagnosis confirmed in 96%, most of whom were symptomatic. Patients in the following categories were screened by genetic testing for hereditary variants whether or not they had a monoclonal gammopathy: 1) blacks were screened for the presence of a mutant transthyretin—the Val122Ile variant of transthyretin occurs in 4% of blacks; 2) patients with dominant peripheral nervous system involvement were screened for hereditary variants—peripheral neuropathy is a common presentation of AL amyloidosis and several hereditary variants; 3) patients with isolated renal amyloidosis and no amyloid in the bone marrow were screened for the fibrinogen Aα variant that occurred in 5% of British patients, all with renal but not marrow amyloid; and 4) patients sent for hereditary screening or with a biopsy reporting amyloidosis were screened for hereditary variants and tested for a monoclonal gammopathy.

Patients with a monoclonal gammopathy and a hereditary variant were identified in three of the four categories, representing 6% of those screened and 2% of symptomatic patients. One was black, one had peripheral neuropathy, and the third was referred for evaluation of hereditary amyloidosis and was diagnosed with Durie-Salmon stage I multiple myeloma. All three had monoclonal gammopathies and a variant transthyretin. Transthyretin tissue staining indicated that in two of the three cases amyloid was likely due to variant transthyretin. These results justify further study of screening for hereditary variants in patients with apparent AL amyloidosis. Problem cases should be referred to centers specializing in amyloidosis for typing and treatment.

FREE LIGHT CHAINS

The recent availability of the FLC assay has changed the way that patients with AL are diagnosed and monitored during therapy [11–13]. The FLC assay provides a direct measure of the fibril-precursor protein. A major problem in treating AL amyloidosis patients has been gauging response and titrating therapy because the response of amyloid disease lags the reduction in the fibril-precursor protein. Therefore, integration of the FLC assay into clinical practice allows the titration of therapy in anticipation of response before evidence of organ improvement may be available. Response of the pathologic FLC level also appears to have prognostic significance after SCT [18].

CARDIAC BIOMARKERS

A role for testing blood levels of brain natriuretic peptide (BNP) and troponin, both chemical markers of myocardial strain and injury, has been established in AL amyloidosis. Cardiac involvement is prevalent in patients with AL amyloidosis at diagnosis, and therefore, these biomarkers are useful in screening [19]. Troponin levels also provide useful information for staging patients at diagnosis, and a staging system using N-terminal proBNP and troponin C has been developed [20•]. The preliminary data strongly suggest that patients with abnormal increases of BNP and troponin have a poor prognosis [21]. These biomarkers may also be of use in the management of patients. The BNP can decrease in cardiac patients when the fibril-precursor FLC is reduced with therapy; however, these tests are nonspecific and can vary as the result of factors other than progression of cardiac amyloid.

Treatment

Diet and lifestyle

- In patients with nephrotic-range proteinuria or cardiomyopathy, the importance of salt restriction to minimize pulmonary and soft-tissue edema cannot be overemphasized. Additional measures to deal with lower extremity edema, such as pressure stockings and keeping the feet elevated when possible, are also recommended routinely.
- Amyloid organ involvement results in loss of vigor and therefore a change of lifestyle. Drugs for erectile dysfunction may be beneficial for some patients. For patients with hepatomegaly and early satiety, taking multiple small meals a day may help to address nutritional needs. Patients who are taking daily diuretics or have chronic orthostasis may experience light headedness on occasion and are instructed to drink two additional 8-oz glasses of water when this happens. In addition, they are told to change position slowly and allow time to equilibrate when seated, with legs dangling before standing.

Therapy

Low-intensity cytoreductive therapy

- The only effective therapeutic approach is to reduce the production of amyloid-forming light chains (Fig.1C). The conundrum of therapy is that minimally toxic treatments that may work gradually are likely to be ineffective because progression of amyloid disease continues.
- Oral melphalan and prednisone were the first beneficial therapy for AL amyloidosis. Phase III trials showed a benefit as compared with placebo [22,23]. Overall, median survival was prolonged from 12 to 18 months,

and response rate was 25%, with a median time to response of 12 months. For patients who survived more than 3.5 years after receiving oral melphalan, there was a 20% of risk of myelodysplasia often leading to secondary leukemia [24]. In a randomized trial, combination chemotherapy was shown to be no more effective in prolonging survival than oral melphalan and prednisone [25].

- The Southwestern Oncology Group conducted a multicenter phase II trial testing pulse dexamethasone, followed by maintenance therapy with dexamethasone and α-interferon, in patients with AL amyloidosis [26]. Hematologic responses were seen in 53% of evaluable patients, with complete remissions in 24%. Organ responses occurred in 45% of patients. Median survival of the entire cohort was 31 months, with estimated 2-year overall and event-free survivals of 60% and 52%, respectively.
- Recently the Italian Amyloidosis Center completed a phase II trial using oral melphalan and dexamethasone in patients with AL amyloidosis not eligible for SCT [27]. This combination of oral agents induced a response in 67% of patients, with a 33% complete response (CR) rate. In 22 (48%) of the responsive patients, organ responses were observed. There were two treatment-related deaths in the first 100 days of therapy, and two patients also subsequently developed myelodysplasia.
- Two small phase I/II clinical trials were conducted testing the toxicity and efficacy of thalidomide in AL amyloidosis. Both demonstrated that thalidomide had significant toxicity and minimal activity [28,29].
- The Italian Amyloidosis Center conducted a phase II trial of thalidomide and dexamethasone combined as salvage therapy [30]. Thalidomide was dosed at 100 mg/day, with increments up to 400 mg, and dexamethasone at 20 mg/day on days 1 to 4 every 3 weeks. Thirty-one patients with AL amyloidosis refractory to or in relapse after first-line therapy were enrolled. Eleven patients (35%) tolerated 400 mg/day thalidomide for a median of 6 months; 14 could take no more than 100 or 200 mg/day for a median of 3 months. Fifteen (48%) achieved a hematologic response, with 19% complete remissions and 26% organ responses; the response rate was higher in those taking higher doses of thalidomide. Overall median time to response was 3.6 months. No cases of cardiac amyloid had organ responses. There were no treatment-related deaths but two thirds of patients experienced severe toxicity. Fluid retention and symptomatic bradycardia without QT prolongation were common adverse reactions, whereas neuropathic and thromboembolic complications were rare.
- Oral melphalan and dexamethasone is the most active regimen based on phase II data. It is easily administered and can be considered equivalent in some respects to melphalan-based SCT, except for the risk of myelodysplasia and secondary leukemia. In those failing melphalan and dexamethasone, thalidomide and dexamethasone should be considered first-line salvage therapy at this time.

Stem cell transplantation

- The effectiveness of SCT in reversing the clinical manifestations of AL amyloidosis in most surviving patients has been documented at numerous centers, and amyloid P component radionuclide scans have demonstrated resorption of AL deposits, with reduction or elimination of the clonal plasma cell disorder that is their root cause [31,32,33•]. As the production of deposits is halted and amyloid resorbed, the performance status and the quality of life of AL amyloidosis patients can improve [34]. Criteria for assessing response have been defined and are in widespread use [35].

- In the largest series of patients reported (n = 312, from a single center), the median overall survival post-SCT was 4.6 years, with 47% surviving at 5 years [36••]. For patients without cardiac involvement at SCT, the median survival was 6.4 years, with 60% 5-year survival, whereas for those with cardiac involvement at SCT, the median survival was 1.6 years, with 29% 5-year survival. Forty-four percent of evaluable patients achieved organ responses at 1 year post-SCT. Complete hematologic response (immunofixation negative) occurred in 40% of patients and was associated with an 82% 5-year survival, compared with 55% for those not achieving CR.
- Although impressive, these summary data include many patients who had been diagnosed more than 12 months before SCT and had been previously treated with oral agents. An element of self-selection is present. A more relevant picture is obtained in the outcomes of a randomized prospective phase II clinical trial of SCT in newly diagnosed patients [37]. Importantly, unlike the overall experience described earlier, all patients enrolled were within a year of diagnosis and not previously treated. Patients (n = 100) were stratified based on organ involvement and time from diagnosis and were then randomized 1:1 to SCT immediately or after two cycles of oral melphalan and prednisone. The endpoints were survival and hematologic and organ responses.
- In this trial, the 100-day treatment-related mortality was 20%, and 12% of patients died in association with stem cell mobilization and collection. There were no significant differences between the two arms with respect to overall survival at a median of 4 years follow-up. At 5 years post-SCT, the overall survival was 50% for immediate and 39% for delayed SCT. The complete hematologic response rates were 21% and 17% (intention-to-treat), and 42% of patients achieved an organ response at 1 year. Fewer patients randomized to oral agents received SCT because of progression of disease making them ineligible for SCT; this affected patients with cardiac involvement disproportionately. Newly diagnosed untreated patients with AL amyloidosis eligible for SCT did not benefit from initial treatment with that combination of oral agents. Overall survival was a function of the number of organ systems clinically affected and the presence of cardiac involvement. For patients with one or two major organ systems affected of heart, kidneys, liver/gastrointestinal tract, and peripheral nervous system, and for those without cardiac involvement, median survival had not been reached at a median of 4 years follow-up. For the others, median survivals in the two groups were 9.3 and 5.2 months, whereas those with cardiac amyloid had median survivals of 9.6 and 4.8 months.
- Refinement of patient selection, application of risk-adapted melphalan dosing, and improvement of peritransplant clinical management have become realities at centers experienced in SCT for AL amyloidosis patients and have resulted in improved outcomes for newly diagnosed patients, compared with the phase II data just recounted [33•,38]. SCT can be safely applied to patients with AL amyloidosis who do not have symptomatic three- or four-organ involvement or advanced cardiac amyloid characterized by recurrent pleural effusions, cardiac syncope, or symptomatic arrhythmias. I recommend that the dose of intravenous melphalan be attenuated based on age and organ involvement (Table 1). This is called a risk-adapted approach, based on the dose-related differences in toxicity observed in clinical trials at different doses of melphalan and on age-related differences in survival [33•,39].
- The trial design of the randomized phase II study described earlier was flawed because a risk-adapted approach was not used, and because the time to response on melphalan and prednisone is longer than 1 year in 30% of cases

Table 1. Guidelines for the use of melphalan and SCT in a risk-adapted manner

Melphalan 200 mg/m^2
Age < 61 years
Symptomatic involvement of no more than two major organ systems with amyloid (of kidneys, liver/gastrointestinal tract, and peripheral/autonomic nervous system)
No cardiac involvement and creatinine clearance ≥ 51 mL/minute
Melphalan 140 mg/m^2
Age < 61 years
With cardiac amyloid that is not advanced* and/or creatinine clearance < 51 mL/minute
Or
Age 61–70 years
Symptomatic involvement of no more than two major organ systems with amyloid, with no cardiac involvement and creatinine clearance ≥ 51 mL/minute
Melphalan 100 mg/m^2
Age 61–70 years with cardiac amyloid that is not advanced and/or creatinine clearance < 51 mL/minute
Or
Age older than 71 years with symptomatic involvement of no more than two major organ systems with amyloid, with no cardiac involvement and creatinine clearance ≥ 51 mL/minute

*Advanced cardiac amyloid is defined as left ventricular ejection fraction < 45%, recurrent pleural effusions requiring thoracentesis, symptomatic cardiac arrhythmias, or cardiac syncope.
SCT—stem cell transplantation.

and only 20% of patients actually achieved hematologic responses. Time to response is an important variable in treating systemic AL amyloidosis. The combination of melphalan and dexamethasone appears significantly more active than melphalan and prednisone. The time to response for melphalan and dexamethasone is 3 months.

- Thus, of great interest in this regard is the phase III trial recently reported by the French intergroup [40]. Although the results of the Italian phase II melphalan and dexamethasone trial were not available to them, these French investigators conducted a randomized prospective phase III multicenter trial (n = 100) in which SCT with standard intravenous melphalan was compared 1:1 with oral melphalan and dexamethasone administered continuously for up to 18 months. The results depict in miniature the learning curve associated with applying SCT to this population of patients. In the SCT group there was a 44% early failure rate largely due to treatment-related deaths (24%) and progression of disease. Analysis of outcomes between the groups demonstrated a center effect in that patients treated at most centers (27 of 29 centers) had much better survival if they received oral therapy ($P < 0.01$), whereas patients in the two centers in which the largest fraction of SCTs were performed had a trend to better survival with SCT. Comparisons of response rates and survival between those alive at least 3 months post-SCT and those who completed at least 3 months of oral melphalan and dexamethasone showed no difference. For both groups, the plasma cell disease response rates were 65%. The organ response rate was higher in the SCT group (52% vs 40%). Median survival was 48 months for SCT and 58 months for oral therapy. Surprisingly, no cases of myelodysplasia were reported in the oral melphalan group.

- Important aspects of the French phase III trial are the clinical concerns raised by the high treatment-related mortality and the impact of center-related effects. (For example, a phase II multicenter SCT trial conducted in the United States had no patients fail to get to SCT and a 10% treatment-related mortality [41].) Additional problems include the fact that the response rate of oral melphalan and dexamethasone was unknown at the time the French trial was designed. The melphalan and dexamethasone regimen was chosen on a theoretical basis; the more rational regimen for the standard therapy group would have been oral melphalan and prednisone, based on prior phase III trials. Moreover, now that we know the response rate with oral melphalan and dexamethasone was 65% in the Italian phase II trial, we know that the French phase III trial was likely underpowered.
- Those issues notwithstanding, the overall survival of patients with AL amyloidosis treated with oral melphalan and dexamethasone has been documented now in two independent trials. The regimen is clearly active and of use for patients not eligible for SCT. The prior experience with melphalan and prednisone also clearly indicates that there is a risk of myelodysplasia and secondary leukemia related to oral melphalan, one that has not been described in association with melphalan use in melphalan-naïve patients in SCT.
- We also maintain that SCT is not simply a solitary modality, as the French trial assumes, but that it provides a robust platform for therapy (as in myeloma) and is an important phase of therapy to which adjuvant treatments can be added in order to improve the overall response rate.
- With that view in mind and with the knowledge that overall survival in AL amyloidosis is linked to response of the plasma cell disease, we conducted a phase II trial prospectively testing a combined approach using risk-adapted melphalan-based SCT followed by adjuvant thalidomide and dexamethasone [42]. Our goals were low treatment-related mortality and optimal hematologic and organ response rates.
- To be eligible, patients had to be untreated and diagnosed within 12 months of enrollment. Patients received autologous SCT with melphalan dosed at 200, 140, or 100 mg/m^2 based on age, renal function, and cardiac involvement (Table 1). Those not achieving a hematologic CR at 3 months post-SCT were treated with 9 months of dexamethasone (20 mg/m^2, one to three pulses monthly) and thalidomide (50–200 mg nightly), or with only dexamethasone if they had prior deep venous thrombosis or neuropathy. Aspirin was used for prophylaxis against thromboembolic complications.
- Forty-five patients (23 men) enrolled, a median of 57 years old (range 34–73 years) and 2 months from diagnosis. Dominant organ involvement was renal in 58% (n = 26), cardiac in 24% (n = 11), and liver/gastrointestinal or peripheral nervous system in 18% (n = 8). A third (n = 15) had two organ systems involved. At baseline, 53% had increased serum BNP, and 21% had increased serum troponin I levels. Dose assignments were 200 (n = 15), 140 (n = 24), and 100 (n = 6) mg/m^2 of melphalan. Treatment-related mortality was 4.4% (2/45). At 3 months post-SCT, 61% of patients had hematologic responses. Persistent clonal plasma cell disease was found in 34 patients; one refused and two were too ill for adjuvant therapy. Twenty-two patients received thalidomide and dexamethasone, and nine received dexamethasone alone. With adjuvant therapy, 48% had an improved response at 12 months, including six who achieved CR. There were no treatment-related deaths in the adjuvant phase, and toxicities were manageable. The hematologic response rate at 12 months was 77%, with 38% CR rate with no significant difference based on the dose of melphalan. Fifty-two percent had organ responses at 12 months,

whereas 29% had stable and 19% had worsened organ function. Only patients who achieved a hematologic response at 12 months had organ responses. With a median follow-up of 20 months, overall survival is 76% and median survival is not yet reached (Fig. 1D).

- Thus, risk-adapted melphalan and SCT have a low treatment-related mortality and with adjuvant therapy post-SCT can improve hematologic response in patients with persistent clonal plasma cell disease. Further study of such combined approaches in AL amyloidosis is warranted, using SCT as a platform for therapy. It would also be reasonable to propose a phase III multicenter trial comparing 12 months of oral melphalan and dexamethasone versus risk-adapted melphalan with SCT plus adjuvant dexamethasone, using response rate at 12 months as the primary endpoint for determination of sample size.

Solid organ transplantation and new approaches

- Young minimally symptomatic patients with hereditary amyloidosis due to variant transthyretin in the United States and Europe are usually deemed candidates for curative solid organ (ie, liver) transplantation in part because of the potential for "domino" transplants [43,44]. That is, the amyloid patient's variant transthyretin-producing liver is used for another recipient. Ironically, at the same time, the use of solid organ transplantation (liver, heart, and kidney) in patients with AL amyloidosis is usually deemed poor risk because of the likely accumulation of amyloid in the grafted organ. However, there have been numerous patients who have successfully undergone cardiac allograft and then SCT; the feasibility of this approach is established, and a phase II trial needs to be performed to demonstrate safety and efficacy in a systematic fashion [45]. Renal transplantation has also been shown to be effective, and renal allografts survive for lengthy periods in many recipients [46].
- All current chemotherapeutic approaches to AL amyloidosis treat the disease by attacking the source of the precursor protein, ie, the clonal plasma cells, and by seeking to reduce their number (Fig. 1C). The development of amyloid-reactive antibodies was based on the premise that an immune reaction to amyloid deposits might help to stimulate fibril disassembly; proof-of-principle was demonstrated in a mouse model with injection of human amyloid extracts into soft tissue sites [47]. The antibody localized within the amyloid depots and caused rapid resolution of this material by an infiltration of neutrophils. The manufacture of a human chimeric form of the antibody is currently underway; the propensity for causing neutrophilic infiltrates and inflammation will likely raise concerns in phase I trial design.
- Hopes for effective agents that resorb deposits in patients have been raised and then lowered on two occasions in the past decade, in part because of the reluctance of investigators to follow traditional steps of clinical development and include a phase I dose-finding stage in the studies, and in part because of disenchantment of the pharmaceutical industry [48–50].

Future directions

- AL amyloidosis remains a disease for which our tests, treatments, and knowledge continue to improve slowly. The FLC assay has improved diagnostic testing and the ability to monitor response to therapy. Developing tests for grading the amyloid-forming potential of specific light chains and making nuclear or other scans for assessing organ involvement widely available are goals for the future.

- Stem cell transplant for AL amyloidosis remains effective in patients with limited disease at centers with experience; it can be risk-adapted in order to optimize benefit and limit mortality, and provides a platform for testing novel post-SCT adjuvant therapies. However, SCT will remain a controversial therapy until there is a phase III trial defining greater benefit with minimal treatment-related mortality. Solid organ transplantation is no less controversial. Hopefully, the sequential use of solid organ transplantation and SCT will also be systematically assessed in clinical trials.
- As we understand more fully the basis of the cellular and organ-specific toxicities of the fibril-precursor light chains, new cytoprotective pathways may be discovered and the promise of simple effective drug treatment fulfilled. New drugs to inhibit deposits from forming or to mobilize them from organs provide prospects that tantalize, despite prior disappointments. The ideal treatment of AL amyloidosis in the future will likely involve a combination approach aimed at eliminating the supply of fibril-precursor light chains, inhibiting light chain self-assembly into fibrils, enhancing organ function, and resorbing existing fibrillar deposits.

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