Treatment of Primary Systemic Amyloidosis (AL): Role of Intensive and Standard Therapy

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Abstract: Immunoglobulin light-chain (AL) amyloidosis is a clonal plasma cell dyscrasia. Delay in diagnosis is the major hurdle in improving the outcomes of AL patients. Almost all patients with systemic AL need cytotoxic therapy. Treatment can improve symptoms and quality of life, as well as extend survival. Supportive care is an integral part of the treatment plan. Severity of cardiac involvement is an important determinant of prognosis and influences the choice of therapy. Cardiac biomarkers and serum free light chain assay are important tools for assessing prognosis and monitoring treatment response. Myeloablative chemotherapy with melphalan and autologous stem cell rescue appears to offer survival benefit; however, it is an option for only a quarter of AL patients. Standard-dose combination chemotherapy with steroids and alkylating agents is a safe and effective treatment strategy that can result in improvement of organ function in many patients. Newer agents such as bortezomib and lenalidomide have shown promising activity and are being evaluated as part of combination regimens in clinical trials.

Keywords
Immunoglobulin light-chain, amyloidosis, chemotherapy, stem cell transplantation

Introduction

Primary systemic or immunoglobulin light-chain (AL) amyloidosis is a protein-folding disorder characterized by tissue deposition of misfolded immunoglobulin light-chains or fragments of light or heavy-chains in fibrillar form.[1] This specific configuration is responsible for the apple-green birefringence observed under polarized microscopic examination of involved tissue stained with Congo red dye—the pathologic hallmark that is essential for the diagnosis of amyloidosis.[2] The source of abnormal protein in AL is a transformed, clonal plasma cell that has low to no proliferative potential.[3]

With an incidence of 8 cases per million per year, AL is a rare disease in the United States.[4] Its diagnosis is frequently delayed due to its nonspecific presenting (general) symptoms and failure on the part of healthcare providers to include it in the differential diagnosis.[4] Clinical and pathologic manifestations of AL result from extracellular deposition of the amyloidogenic immunoglobulin protein that causes direct cell toxicity and pressure atrophy of involved organs, thereby resulting in organ failure.[3] The heart is the most important organ commonly involved in AL patients. Other organs frequently involved include the kidney, peripheral nerves, gastrointestinal tract, lung, liver,

Table 1. Findings Associated With Adverse Outcomes in AL Amyloidosis

Prognostic Factor	Comment
Clinical Findings	
Congestive heart failure and exertional syncope	Patients presenting with exertional syncope have a median survival of 2 months
Jaundice	Jaundice and hyperbilirubinemia is usually a preterminal finding
Laboratory Findings	
Hyperbilirubinemia	Often a preterminal finding
Thrombocytosis	
Elevated creatinine	
Elevated free light chain levels	Important factors that have been incorporated into a 4-stage prognostic model
Elevated troponin T	
Elevated BNP (NT proBNP)	
Echocardiogram Findings	
Interventricular septum thickness	Median survival is 1 year with a thickness of >1.5 cm and 4 years with a thickness of <1.5 cm
Short mitral deceleration time	Poor outcome for patients with deceleration <150 ms
Decreased fractional shortening	Poor outcomes for patients with fractional shortening <20%

AL=immunoglobulin light-chain; NT proBNP=N-terminal fragment B-type natriuretic peptide.

and spleen.[5] Traditionally, the outcome of AL patients has been poor, primarily because of delays in diagnosis. Recent data suggest that with earlier recognition, improvements in disease monitoring and organ function assessment, and availability of effective therapies, the survival of AL patients has improved in the last 3 decades.[6]

This article will review the evolution of treatment paradigms in AL amyloidosis, with a focus on intensive and standard treatment strategies, various therapeutic challenges faced by AL patients, and the role of supportive therapy. Factors that influence treatment selection and the future clinical directions of the disorder will be summarized.

Management of AL

Once a diagnosis of AL is confirmed histologically, the next step is to inform the patient about prognosis and discuss supportive and cytotoxic treatment with a clear understanding of its aims and objectives. The ability to predict the outcomes of patients with AL has significantly improved over the last several years. Various clinical, laboratory, and imaging findings that have been shown to influence the prognosis of AL patients are summarized in Table 1.

The most important organ involved with AL is the heart, and the extent of cardiac involvement determines the prognosis. With the widespread availability of biomarkers of cardiomyocyte damage—the troponin T and the pro-hormone N-terminal fragment B-type natriuretic peptide (NT-proBNP)—a 3-stage prognostic system was developed that helped predict survival in AL. Patients with stage I (both markers low), stage II (1 marker high and 1 low), or stage III (both markers high) had median survivals of 26.4 months, 10.5 months, and 3.5 months, respectively.[7] Recently, serum free light chain assay (SFLA) has proven invaluable in the biochemical assessment of plasma cell dyscrasias.[8] In AL amyloidosis, SFLA not only has a prognostic value, but it is also the most important tool to monitor response to therapy and predicts outcomes after treatment.[9] Based on an evaluation of 810 patients with newly diagnosed AL, our group at Mayo Clinic incorporated SFLA into a prognostic model that includes cardiac troponin T and NT-proBNP and is able to separate the survival into 4 distinct groups (stages) that range from 94.1 months to 5.8 months for stage I and stage IV disease, respectively (Figure 1).[10]

Many patients with amyloidosis present with advanced disease with involvement of more than 1 organ, which significantly shortens survival and reduces quality of life.[11] It is imperative to institute organ-directed supportive measures that may range from those that provide rapid, symptomatic relief (eg, diuretics for congestive heart failure) to those that improve quality of life and potentially extend survival (eg, implantable cardioverter defibrillator and pacemaker, cardiac or renal transplant).

AL-Specific Systemic Therapy

Almost all patients with AL amyloidosis need systemic therapy. Studies have shown that treatment improves organ function, quality of life, and survival of AL patients. In a recent analysis of AL patients evaluated at Mayo Clinic between 1977 and 2006, we noted improvement in 4-year survival during each successive decade of this period (21%, 24%, and 33%, respectively).[6] However, mortality in the first 6 months has not improved in 30 years.

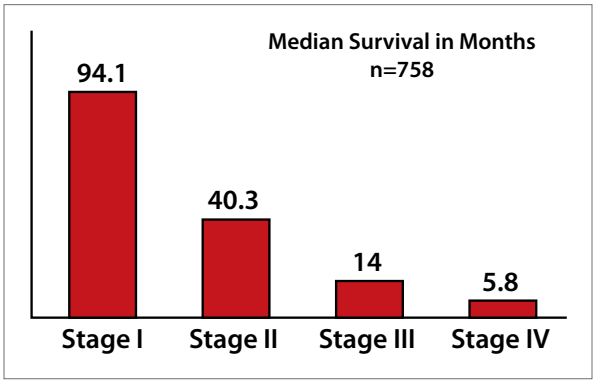

Figure 1. Revised prognostic score utilizing serum free light chain assay measurements derived from 758 previously untreated immunoglobulin light-chain (AL) amyloidosis patients seen at Mayo Clinic. One point was given for each of the following factors: difference between involved and uninvolved free light chain ≥18 mg/dL, cardiac troponin T ≥0.025 ng/mL, and N-terminal fragment B-type natriuretic peptide ≥1,800 pg/mL. Patients were assigned to stages based on the number of points: 0 points to stage I (n=189; 25%), 1 point to stage II (n=206; 27%), 2 points to stage III (n=186; 25%), and 3 points to stage IV (n=177; 23%). This figure was created with permission from Kumar S et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol*. 2012;30:989-995.

Current treatment of AL focuses on the use of antineoplastic agents directed against the clonal plasma cell that is the source of the amyloidogenic immunoglobulin, and therefore it comes as no surprise that the field of AL therapeutics has followed the progress in multiple myeloma (MM), a common plasma cell malignancy with an incidence five-fold higher than that of AL amyloidosis. It is imperative to realize that unlike in MM, where the tumor burden of proliferative neoplastic plasma cells drives the clinical course, the natural history of AL is determined by the degree and type of solid organ involvement by the amyloidogenic protein produced by nonproliferating transformed plasma cells. These critical differences in the disease pathophysiology and natural history are, in large part, responsible for the generally poor outcome of AL patients and some of the challenges unique to AL treatment, thus making its management a highly specialized one.

One of the unique challenges in the management of AL patients had been monitoring the response to therapy.[12] In the past, this proved difficult as the parameters of response assessment involved testing that was variably—and at times poorly—quantifiable, such as serum and urine protein electrophoresis and immunofixation electrophoresis, and bone marrow plasma cell response. Assessment of organ responses was difficult because these responses take a long time to manifest. Although iodine-labeled serum amyloid P component scanning is utilized in some centers in Europe to estimate amyloid protein burden in various organs, it cannot assess cardiac involvement and is not available in the United States. SFLA and cardiac biomarkers, in addition to predicting prognosis, have proven invaluable as objective parameters to characterize and monitor the response to treatment.[12,13] These tests have become instrumental in the design of new clinical trials and will aid in the comparison of results across different studies. A consensus definition of organ involvement and treatment response incorporating the SFLA was developed at the Tenth International Symposium on Amyloid and Amyloidosis.[13]

Against this background, we review the role of stem cell transplant and standard-dose systemic therapy in the treatment of AL. It is important to recognize that the majority of the available evidence relies on studies conducted at single centers with variable patient selection criteria. Such variations are reflected in the disparate results seen with similar therapeutic interventions conducted at different centers.

Nonintensive Chemotherapy for AL

Conventional chemotherapy agents That AL is a treatable condition was first demonstrated in the early and mid 1970s, when melphalan (Alkeran, GlaxoSmithKline)as a single agent was shown to improve nephritic-range proteinuria in AL patients.[14] After the success of the melphalan and prednisone regimen in MM, this combination was also evaluated in AL. Two randomized clinical trials comparing the combination of melphalan and prednisone with colchicine noted approximately a doubling of median survival with the melphalan/prednisone regimen (17 months vs 8.5 months in 1 study and 12.2 months vs 6.7 months in the other).[15,16] In one study, multivariate analysis demonstrated that melphalan significantly impacted survival in patients who did not have heart failure. In a review of the Mayo Clinic experience with this regimen, we noted an overall response rate of 18%.[17] While responses were noted even in patients with heart involvement, the best response was seen in patients who had only nephrotic syndrome with preserved renal function.

With the recognition of the antimyeloma activity of dexamethasone, a small study evaluated this agent at a dosage of 40 mg daily on days 1–4, 9–12, and 17–20 every 5 weeks (high-dose regimen) in 9 AL patients.[18] Organ improvement was observed in 8 of 9 patients. In our experience at Mayo Clinic, single-agent, high-dose dexamethasone in patients who had failed melphalan or who had not received treatment with it was effective, but

the toxicity at this dose (eg, fluid retention, metabolic complications, and gastrointestinal bleeding) was prohibitive for prolonged use.[19,20] Using a modified schedule that reduces total dexamethasone dosage per cycle, Palladini and colleagues noted a hematologic complete remission (CR) rate of 24% in a group of 93 patients with AL.[21] The median survival of this group was 31 months, and organ improvement was noted in 43% of patients.

Although dexamethasone has not been compared in a head-to-head trial with prednisone, it has been widely adopted in combination regimens for AL. Therefore, it was evaluated in combination with melphalan in both high-dose and low-dose regimens in AL. An Italian study combining melphalan with high-dose dexamethasone noted an impressive hematologic response rate of 67% in 46 previously untreated AL patients who were not candidates for high-dose therapy and stem cell rescue.[22] A third of the patients achieved hematologic CR, and organ improvement was noted in 48% of patients. A very important finding of this study was a strong correlation between the depth of hematologic response and improvement in organ function. Maximum organ improvement (87%) was seen in patients with hematologic CR, and no improvement was noted in nonresponders. In another study, weekly dosing of dexamethasone was found to be similar to the 4-day schedule in combination with melphalan.[23]

Novel agents The last decade has seen the introduction of immunomodulatory drugs (IMiDs) and proteasome inhibitors into clinical practice, which has transformed the management of multiple myeloma. Evolving experience with these agents in AL is encouraging, and ongoing clinical trials are evaluating their role in its management.

IMiDs such as thalidomide, lenalidomide (Revlimid, Celgene), and, most recently, pomalidomide (Kyprolis, Onyx) have been evaluated in AL. Experience with thalidomide has been less than optimal, primarily due to its poor tolerability. In a study of 16 AL patients treated with thalidomide, adverse events of grade 3 or higher were noted in 50% of patients, and exacerbation of neuropathy and congestive heart failure was frequent.[24] When used in combination with dexamethasone and cyclophosphamide, thalidomide resulted in high hematologic response rates (74%), but the toxicity was significant.[25]

Lenalidomide has also demonstrated activity in AL, both as a single agent and in combination with steroids and alkylating agents. Initial experience suggests that it is better tolerated than thalidomide and is capable of producing durable responses. In a phase II study of 35 patients, lenalidomide was used as a single agent at a dose of 25 mg/day on 21 of 28 days. Dexamethasone was added if no responses were observed.[26] Eight of 13 evaluable patients had a hematologic response. The dose of lenalidomide was reduced to 15 mg/day due to rash, fatigue, and other side effects noted in the first 6 patients. Lenalidomide has also shown activity in patients who had progression of disease after melphalan, bortezomib (Velcade, Millennium), and thalidomide.[27] The triplet combination of lenalidomide, dexamethasone, and melphalan was evaluated in newly diagnosed AL patients in a multicenter, phase I/II trial.[28] This regimen demonstrated impressive activity, with hematologic CR achieved in 42% of patients.[28] Similar results were seen when lenalidomide was combined with cyclophosphamide and dexamethasone in a phase II study at Mayo Clinic.[29]

Pomalidomide is a very potent analog of thalidomide and lenalidomide. Its toxicity profile compares favorably to other IMiDs. In a phase II trial, Dispenzieri and coworkers evaluated the safety and efficacy of pomalidomide in combination with dexamethasone in 29 patients with previously treated AL.[30] With an overall response rate of 38%, three-fourths of the patients were alive at 1 year, and 56% were free of disease progression. The majority of these patients had previously received high-dose melphalan, bortezomib, thalidomide, or lenalidomide. These data suggest that IMiDs are active in patients with AL and are capable of inducing durable remissions; however, toxicity of these drugs is significant, and doses routinely used to treat MM may not be well tolerated.

Bortezomib, the first-in-class inhibitor of the proteasome, has also been evaluated in previously treated and untreated AL patients. A significant advantage of bortezomib is its ability to rapidly decrease the burden of amyloidogenic light chain (with a median time to response of less than 2 months). In a phase II study, 14 of 18 patients (77%) with relapsed/refractory AL had a hematologic response, 16% of which were CRs.[31] Both weekly and twice-weekly schedules of bortezomib have been investigated in patients with relapsed/refractory AL in a phase I study.[32] No significant differences were seen in response rates or 1-year progression-free survival between the 2 schedules of administration. Treatment discontinuations and dose reductions were more frequent with the twice-weekly schedule. The authors concluded that both dose schedules appeared feasible and effective. Bortezomib has also been combined with dexamethasone in a multicenter, phase II trial.[33] Hematologic response was noted in 71% of patients, and 25% achieved a CR. Previously untreated patients had a CR rate of 47%. Similarly high overall and complete response rates (52% and 31%, respectively) were noted in another phase II trial that evaluated the combination of bortezomib and dexamethasone.[34] A notable finding from this 26-patient study was relatively short progression-free survival (5 months) and overall survival (18.7 months), which raises concerns about the durability of response with this regimen. Bortezomib-

Table 2. Use of Newer Agents in AL Amyloidosis: Special Issues

Novel Agent	Comments
IMiDs	All IMiDs have the potential to increase BNP (proBNP), and response should be interpreted with caution
Thalidomide	Neurotoxicity and cardiotoxicity of thalidomide is significant
Lenalidomide	Rash and fatigue is prominent with lenalidomide
	Lenalidomide and thalidomide doses used to treat myeloma are often not tolerated in AL
Pomalidomide	
Proteasome Inhibitors	
Bortezomib	Bortezomib results in rapid reduction in light chains
	Can be given weekly or twice weekly and in patients with renal insufficiency
	Should be used cautiously in stage III disease and advanced cardiac involvement
MLN 9708	Oral proteasome inhibitor, under early-phase investigation for patients with AL

AL=immunoglobulin light-chain; BNP=B-type natriuretic peptide; IMiD=immunomodulatory drug.

based regimens are being evaluated as part of induction and consolidation therapy in AL patients undergoing stem cell transplantation.

The widespread availability of these new and effective agents has significantly increased the therapeutic options for AL patients. It is too early to conclude that these agents should replace the alkylator and steroid combination as the standard of care, especially as a survival benefit has not been demonstrated. The only way to answer this question is to systematically compare these treatments in the setting of randomized controlled clinical trials. Various novel agents being evaluated for the treatment of AL amyloidosis are listed in Table 2.

Stem Cell Transplantation for AL

Hematopoietic stem cell transplantation is an effective treatment for many hematologic malignancies, including multiple myeloma; therefore, it seemed logical to explore this approach in the treatment of AL. The clinical experience suggests that mortality and morbidity of stem cell transplantation is much higher in AL compared to other disorders. It is important to recognize the unique challenges faced by AL patients in the context of stem cell transplantation. Although patients with AL, unlike other hematologic malignancies, do not have clinically significant cytopenias, they have significant involvement of vital organs (heart, kidney, liver, and gastrointestinal tract) that compromises their performance and functional status, and puts them at higher risk of side effects from high-dose therapy.

Although both allogeneic and autologous peripheral blood progenitors have been used as a source of stem cells after myeloablative chemotherapy for the treatment of AL, the majority of experience is derived from the use of autologous stem cells as a rescue. The European Group for Blood and Marrow Transplantation reported outcomes of 15 AL patients who underwent myeloablative (n=7) and reduced-intensity conditioning (n=8) using allogeneic stem cells. CR was noted in 8 patients.[35] Chronic graft-versus-host disease was reported in 5 of 7 evaluable patients in CR. The treatment-related mortality was 40%, with only 53% of patients free of progression at 1 year.

Since the publication of the first report using high-dose chemotherapy and autologous peripheral blood stem cell rescue, several centers have reported their experience. In their study of 25 patients, Comenzo and colleagues reported a hematologic response of 62% and an organ response of 65% in surviving (evaluable) patients.[36] A report from the Amyloid Treatment and Research Program at Boston University School of Medicine and Boston Medical Center evaluated 250 AL patients who underwent high-dose melphalan and autologous peripheral blood stem cell rescue.[37] Two-thirds of the patients were alive at a mean follow-up of 23 months. Early mortality (by 3 months) was high (14%), and 11% of patients could not undergo stem cell transplantation after initiating mobilization due to death or toxicity. Major toxicities included cardiac arrest (n=10), febrile neutropenia (n=62), gastrointestinal tract hemorrhage (n=17), and renal failure requiring dialysis (n=12).

Published data from Europe also highlight a very high early mortality in patients undergoing high-dose therapy. A French report detailing the experience in 21 AL patients undergoing stem cell transplant noted first-month post-transplant mortality of 43%, with most deaths attributed to multiorgan failure.[38] Similarly, a report from Britain noted early treatment-related mortality of 30% in 27 AL patients undergoing high-dose therapy and autologous peripheral blood stem cell rescue.[39] The most common causes of death were multiorgan failure, gastrointestinal tract hemorrhage, sepsis, and cardiac complications. Despite the high mortality rate, a majority of surviving patients responded to therapy in both studies. These data highlight the importance of patient selection before use of high-dose therapy.

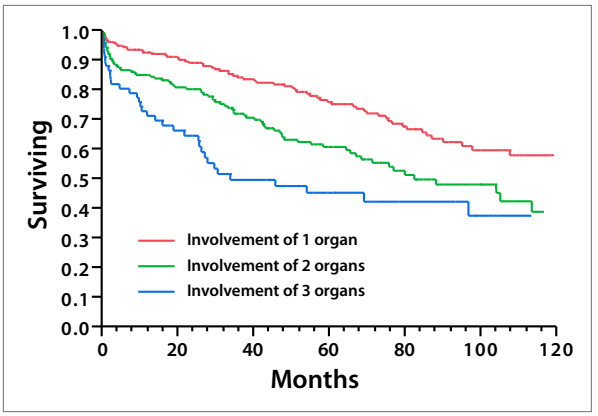

Figure 2. Survival in immunoglobulin light-chain (AL) amyloidosis patients undergoing stem cell transplantation at Mayo Clinic (N=507) according to the number of involved organs: 1 organ (n=245), 2 organs (n=195), or 3 organs (n=67). Median survival for the group with involvement of 1 organ was not reached (58% at 10 years). Median survival was 82.3 months for patients with involvement of 2 organs and 33.7 months for patients with involvement of 3 organs. The median overall survival for all 507 patients was 107.5 months.

We have published our experience with stem cell transplantation in 434 patients with AL at Mayo Clinic.[40] The majority of patients had involvement of 2 or more organs. We noted a hematologic response rate of 75% and a CR rate of 38%. Organ response was observed in 46% of patients. Quality of hematologic response to induction and disease stage were the most important predictors of outcome. Median survival was not reached for patients who achieved CR, while it was 107 months for those with partial remission and 32 months for nonresponders. Patients with involvement of more than 2 organs had a median survival of 33.7 months, compared to 82.3 months in those with involvement of 2 organs (Figure 2). Analysis of patients in whom the data on pretreatment NT-proBNP levels were available demonstrated a significant impact of NT-proBNP levels greater than 170 pg/mL. Relatively longer survival in nonresponders compared to an unselected nonresponding population not undergoing transplantation probably reflects selection bias because patients who do not have advanced organ damage (which inherently indicates good-risk disease) were chosen to undergo stem cell transplantation.[41] We now report an early (within 100 days of transplant) mortality of 9%. Multiorgan failure was the most common cause of mortality. In our experience, stem cell mobilization was easily achieved with administration of granulocyte colony stimulating factor (G-CSF) at a median of 7.16 million cells/kg body weight. We did not routinely use G-CSF to support engraftment due to the concern for weight gain, and the engraftment kinetics was predictable. Of note, 20% of patients completed the entire procedure as outpatients.

Table 3. Contraindications to Stem Cell Transplant

Absolute Contraindication
Clinical congestive heart failure
Total bilirubin >3.0 mg/dL
Echocardiographic ejection fraction <45%
Troponin T >0.06 ng/mL
Relative Contraindication
Serum creatinine >2.0 mg/dL
Interventricular septal thickness >15 mm
Age >65 years
More than 2 visceral organs involved

Several prognostic factors for survival after stem cell transplantation have been recognized. The ones with the most relevance and clinical utility include depth of hematologic response; number of involved organs; interventricular septal thickness on echocardiogram; serum levels of creatinine, troponin T, and NT-proBNP; free light chain levels, and excessive weight gain during stem cell mobilization.

Intensive Versus Standard Therapy in AL

An important question that remains largely unanswered is whether high-dose therapy with stem cell transplant is better than standard-dose treatment. The only way to answer this question in a definitive way is to conduct a randomized controlled trial of the 2 modalities. The only prospective controlled trial conducted to answer this question was a French trial that randomly assigned 100 patients with AL amyloidosis to high-dose therapy or standard therapy with melphalan and dexamethasone.[42] This study did not identify any notable differences between the therapies in regard to response rates (65% for the standard group vs 64% for the high-dose group) or median survival (57 months in the standard group vs 49 months in the high-dose group). The results of this study must be interpreted with caution. Although high early mortality (24%) was seen in the transplant group, it was likely due to poor patient selection. A meta-analysis of high-dose therapy in AL patients also did not identify any significant survival advantage with stem cell transplant.[43] We believe that this outcome is due to inherent bias in individual studies caused by suboptimal patient selection.

A report from Boston described long-term outcomes of AL patients who underwent high-dose therapy and stem cell rescue.[44] Ten-year survival was

Table 4. Risk-Adapted Approach for Patients Undergoing Stem Cell Transplant

Low Risk (all of the following)		
1 or 2 organs involved No cardiac involvement Creatinine clearance ≥51 mL/min Any age		
Intermediate Risk (all of the following)		
Age <61 years 1 or 2 organs involved Asymptomatic cardiac or compensated cardiac involvement Creatinine clearance <51 mL/min		
High Risk (1 of the following)		
3 organs involved* Advanced cardiac involvement		
Melphalan Dosage (mg/m²) Based on Risk Group and Age		
Low Risk	**Intermediate Risk**	**High Risk**
200 if age ≤60 years 140 if age 61–70 years 100 if age ≥71 years	140 if age ≤50 years 100 if age 51–60 years –	Standard therapy Clinical trials –

*Organ involvement includes heart, kidney, nerves, liver, and vascular or soft tissue; it does not include involvement of bone marrow, skin, tongue, or gastrointestinal tract.

This research was originally published in *Blood*. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. *Blood*. 2002;99:4276-4282. © The American Society of Hematology.

reached by 25% of patients. Long-term survival prior to the advent of high-dose therapy was reported to be 4%.[45] In a case-matched control study comparing 63 AL patients who underwent stem cell transplantation with 63 patients matched for age, sex, cardiac function, creatinine level, and proteinuria who did not undergo intensive therapy, our group at Mayo Clinic noted a survival advantage for patients who underwent stem cell transplantation.[46] In a recent analysis, we noted 10-year actuarial survival of 45% in 492 AL patients who underwent high-dose therapy and stem cell rescue at Mayo Clinic.[47]

Our Recommendations

The above discussion demonstrates that high-dose therapy in AL is a very effective treatment capable of inducing high response rates of good quality. Early mortality from the treatment is significant and has varied in studies from 10–43%. We believe that the high mortality rate in some studies is due to bias in the selection of patients. In our opinion, careful patient selection is key to reducing treatment-related mortality from transplant. At Mayo Clinic, if a patient has clinical congestive heart failure, bilirubin greater than 3.0 mg/dL, left ventricular ejection fraction of less than 45%, or a troponin T level of greater than 0.06 ng/mL, we recommend against stem cell transplantation[48] (Table 3). For patients older than 65 years, who have serum creatinine of more than 2 mg/dL, interventricular septum thickness exceeding 1.5 cm, or involvement of 2 or more organs, eligibility for transplant is determined on a case-by-case basis. A risk-adapted approach routinely used by us to help determine the risk and the dose of the conditioning regimen for stem cell transplantation is summarized in Table 4.

Based on our experience and the review of available evidence, we conclude that:

- Almost all patients with AL amyloidosis should be offered treatment, as it improves quality of life and can prolong survival. Our first consideration is always for well-designed clinical trials that aim at answering critical questions.
- Stem cell transplantation is an effective treatment for a minority (20–25%) of patients with primary systemic amyloidosis and should be offered to such patients who fulfill the stringent criteria for selection.
- Treatment regimens incorporating novel agents must be evaluated in prospective randomized trials before their generalized use is considered standard.

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