

# High Dose Melphalan and Autologous Peripheral Blood Stem Cell Transplantation in AL Amyloidosis

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## KEYWORDS

- AL amyloidosis • Stem cell transplantation • Melphalan • Supportive care
- Treatment-related mortality • Patient selection

## KEY POINTS

- High-dose melphalan (HDM) and autologous peripheral blood stem cell transplantation (SCT) can lead to durable remissions and long-term survival in AL amyloidosis.
- The morbidity and mortality of HDM-SCT in AL amyloidosis patients can be minimized with careful patient selection and center experience.
- Survival strongly depends on achievement of a hematologic complete response and patients with less organ involvement and absence of cardiac involvement do better.
- Continued efforts to refine patient selection and management, and incorporate novel anti-plasma cell agents in combination or sequentially, should further improve prognosis in AL amyloidosis.

## INTRODUCTION

The amyloidoses are a group of diseases that share a common feature of extracellular deposition of pathologic, insoluble, fibrils in many tissues and organs. These fibrils have a characteristic beta-pleated sheet configuration that stains with the Congo red dye, producing apple green birefringence under polarized light microscopy.<sup>1</sup> Classification of the amyloidoses is based on the precursor protein that forms the amyloid fibrils, and the distribution of amyloid deposition (systemic or localized).<sup>2</sup>

AL amyloidosis (ie, immunoglobulin light chain amyloidosis) is the most common form of systemic amyloidosis in the United States and Europe. Although AL amyloidosis is considered an uncommon disease, it has an incidence similar to

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Hodgkin lymphoma or chronic myelogenous leukemia.<sup>3</sup> It affects 5 to 12 persons per million per year, although autopsy studies suggest that the actual incidence might be higher. The annual incidence of AL amyloidosis in Olmstead County, Minnesota, is 8 in a million patients.<sup>4</sup> The amyloidogenic precursor protein in AL amyloidosis is an immunoglobulin light chain or a fragment of light chain, usually the variable region, produced by the clonal plasma cell population in the bone marrow. The plasma cell burden in this disorder is usually low (5%–10%), although AL amyloidosis can be associated with multiple myeloma in 10% to 15% of cases.<sup>5</sup>

### TREATMENT TARGETS

A detailed elaboration of the pathogenesis of AL amyloidosis is beyond the scope of this article. However, each of the steps in the pathogenesis of amyloidosis, from the production of the precursor protein to formation of amyloid deposits, is a potential target for treatment.<sup>6</sup> Preclinical and clinical studies are being designed or are ongoing for several of these targets. Reducing the amyloidogenic precursor protein (ie, light chains produced by the clonal plasma cell dyscrasia) with chemotherapeutic agents has been used for the past several decades. Several interventions aimed at facilitating degradation of the amyloid deposits have been reported in AL amyloidosis. A detailed description of all the treatment options is beyond the scope of this article, which is focused on targeting the clonal plasma cell dyscrasia.

### TREATMENT: GENERAL PRINCIPLES

The keys to effective treatment of AL amyloidosis are early diagnosis and correct typing. Ideally, treatment should be started before irreversible organ damage has occurred. Once the diagnosis of AL has been firmly established, the design of the therapeutic strategy depends on a fine balance between the efficacy of the chosen regimen and the individual patient's expected ability to tolerate the toxicity of the treatment regimen, especially in the setting of cardiac involvement with amyloidosis. The current therapeutic approach to systemic AL amyloidosis is based on the observation that organ function is restored if the synthesis of the amyloidogenic protein precursor is shut down. Therefore, the aim of therapy is to rapidly reduce the supply of misfolded amyloid-forming monoclonal free light chains by suppressing the underlying plasma cell dyscrasia while using supportive measures to preserve target organ functions.

### MONITORING THE THERAPEUTIC EFFECT

The criteria for hematologic and organ responses have been unified, formalized, and recently updated at the XIth International Symposium on Amyloidosis.<sup>7,8</sup> Hematologic response usually translates into clinically improved organ function and is associated with a substantial survival advantage and improved quality of life. However, if the organ damage is advanced, it may be irreversible despite hematologic remission. Most patients with a hematologic response show a clinical response after 3 to 6 months, although late responses have been observed. Even though partial hematologic responses can be beneficial, it seems that significant reductions in free light chain levels are associated with the best clinical responses.<sup>9,10</sup> However, the rate of clinical response is higher in patients with a complete hematologic response than in those with a partial one.

## INITIAL PILOT STUDIES OF HIGH-DOSE CHEMOTHERAPY AND STEM CELL TRANSPLANTATION IN AL AMYLOIDOSIS

Intravenous high-dose melphalan (HDM) chemotherapy and autologous peripheral blood stem cell transplantation (SCT) has been successful in inducing complete hematologic remissions and prolonging survival in multiple myeloma.<sup>11,12</sup> Therefore, it was logical to apply this approach to the treatment of AL amyloidosis. The Amyloid Research and Treatment Program, now called the Amyloidosis Center, at Boston University School of Medicine, has a long-standing investigative interest in the pathophysiology and treatment of the various forms of systemic amyloidoses. In 1994, a multidisciplinary clinical group was formed at Boston University Medical Center to develop high-dose chemotherapy protocols for AL amyloidosis. This group was made up of clinicians allied with the Amyloid Research and Treatment Program, representing the disciplines of cardiology, nephrology, pulmonology, neurology, gastroenterology, and rheumatology, together with hematologists in the Stem Cell Transplant Program of the Section of Hematology and Oncology and clinical pathologists from the Apheresis and Blood Bank.

The initial experience with HDM-SCT in 5 subjects with AL amyloidosis was reported in 1996.<sup>13</sup> This pilot study showed that AL amyloidosis subjects with significant systemic disease could be successfully treated with HDM-SCT. Furthermore, 3 of the 5 subjects achieved a complete hematologic response (CR), with disappearance of their underlying clonal plasma cell disorder following treatment. Moreover, all 5 subjects experienced reversal of amyloid-related organ dysfunction.

## CUMULATIVE EXPERIENCE OF HIGH-DOSE MELPHALAN AND STEM CELL TRANSPLANTATION AT A SINGLE CENTER

An expanded series with 312 subjects was conducted by the Amyloidosis Center in 2004.<sup>14</sup> Hematologic complete response (CR) occurred in 40% of evaluable subjects and 66% of the subjects achieved improvement in at least 1 organ function with a hematologic CR. Moreover, the median survival was 4.6 years for this cohort.

The long-term follow-up of 80 subjects treated in the first 3 years of the program (1994–1997) was reviewed.<sup>15</sup> The early death rate, within 100 days of SCT, was 14%. Hematologic CR was achieved by 51% (32 of 63) and the median survival was 4.75 years. The median survival exceeded 10 years for subjects achieving a CR after HDM-SCT, compared with 50 months for those not achieving a CR. The long-term survival beyond 10 years was achieved in 23.5% (95% CI, 15% and 33%) of subjects with AL amyloidosis treated with HDM-SCT. Hematologic relapses occurred in 34% (n = 11/32) subjects at a median time of 2.5 years (range 2–8).

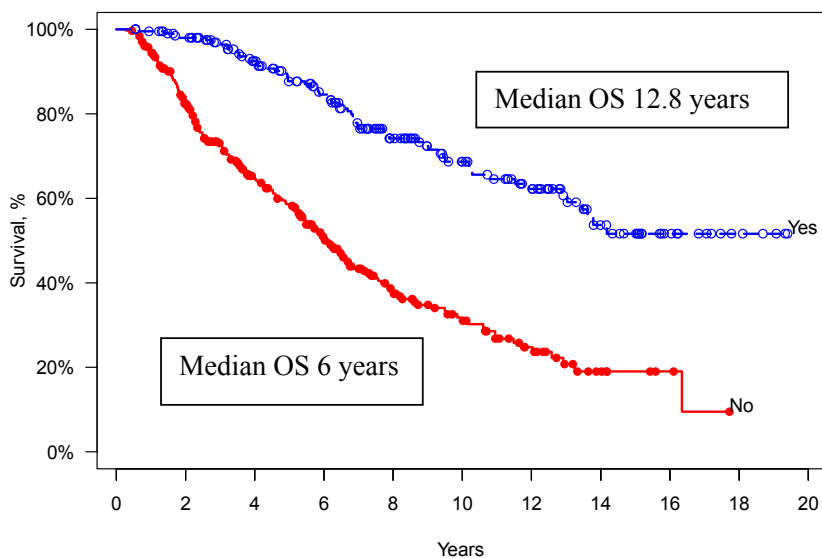
Recently, the outcomes of 421 subjects treated with HDM-SCT from July 1994 to December 2008 were analyzed.<sup>16</sup> Treatment-related mortality was 11% overall and decreased to 6% in the last 5 years. For this group, the median event-free survival (EFS) and overall survival (OS) were 2.6 and 6.3 years, respectively. Of 340 subjects evaluable at 1 year beyond HDM-SCT, 43% achieved a CR and 78% of them experienced an organ response. For CR subjects, median EFS and OS were 8.3 and 13.2 years, respectively. Among the 195 subjects who did not obtain CR, 52% reached an organ response, and the median EFS and OS were 2 and 5.9 years, respectively. A subgroup of 26% of the non-CR subjects remained clinically stable at 5 years of follow-up. Hematologic relapses occurred in 40 subjects (28%) at a median time of 3.7 years (range, 1.5–12.7).

Most recently, long-term outcomes of 607 subjects with AL amyloidosis undergoing HDM-SCT from July 1994 to Aug 2013 were analyzed. The median age was 57 years.

Of these, 53% had cardiac involvement and 41% had multiorgan involvement. Treatment-related mortality was 9% and 80% of the deaths were associated with cardiac involvement. Hematologic CR was achieved by 34% by an intention-to-treat analysis. Hematologic CR was 45% for those who received 200 mg/m<sup>2</sup> of melphalan compared to 33% for those who received 100 to 140 mg/m<sup>2</sup> melphalan ( $P = .02$ ). The median OS was 6.7 years. The median OS was significantly better for those who achieved a hematologic CR, for those without cardiac involvement, and for those with less than 2 organ systems involvement (Figs. 1–3). Hematologic relapses occurred in 20% of subjects with hematologic CR at a median of 4 years (range 1.6–12.4 years).

### ELIGIBILITY CRITERIA FOR HIGH-DOSE MELPHALAN AND STEM CELL TRANSPLANTATION

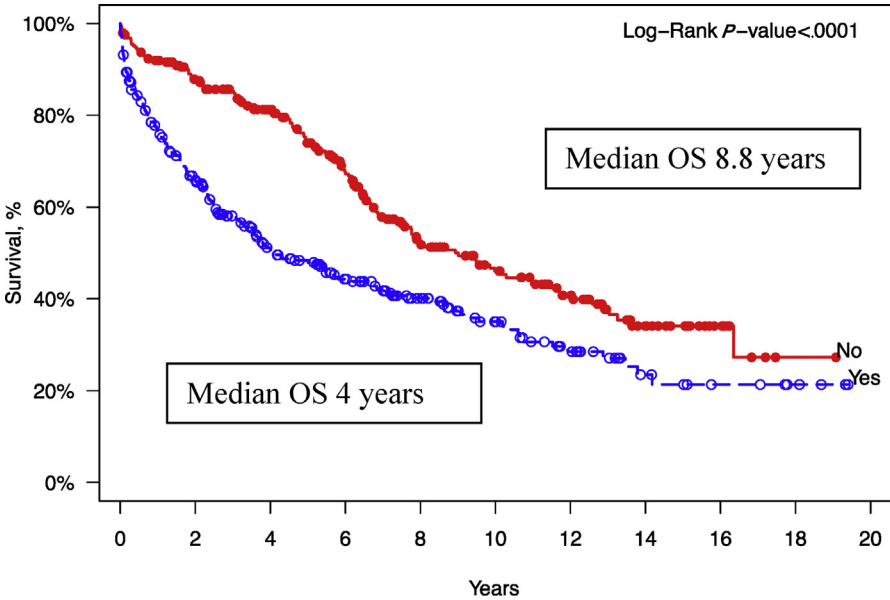
The Amyloidosis Center eligibility criteria for treatment with HDM-SCT are a confirmed tissue diagnosis of amyloidosis, clear evidence of a clonal plasma cell dyscrasia, age greater than 18 years, and minimum measures of performance status (Southwest Oncology Group [SWOG] 0–2), cardiac function (left ventricular ejection fraction >40%), pulmonary function (oxygen saturation >95% on room air), and hemodynamic stability (baseline systolic blood pressure >90 mm Hg). Patients on hemodialysis or peritoneal dialysis for renal failure are not excluded if other eligibility criteria are met.<sup>14</sup> The dose of melphalan can vary from 100 to 200 mg/m<sup>2</sup> based on the risk-adapted approach, described by Comenzo and Gertz,<sup>17</sup> to reduce treatment-related morbidity and mortality associated with HDM-SCT. The patients can be stratified into 3 risk categories: (1) good-risk patients are of any age and have 1 to 2 organs involved, no cardiac involvement, and creatinine clearance greater than 50 mL/min; (2) intermediate-risk patients



Patients, *n*

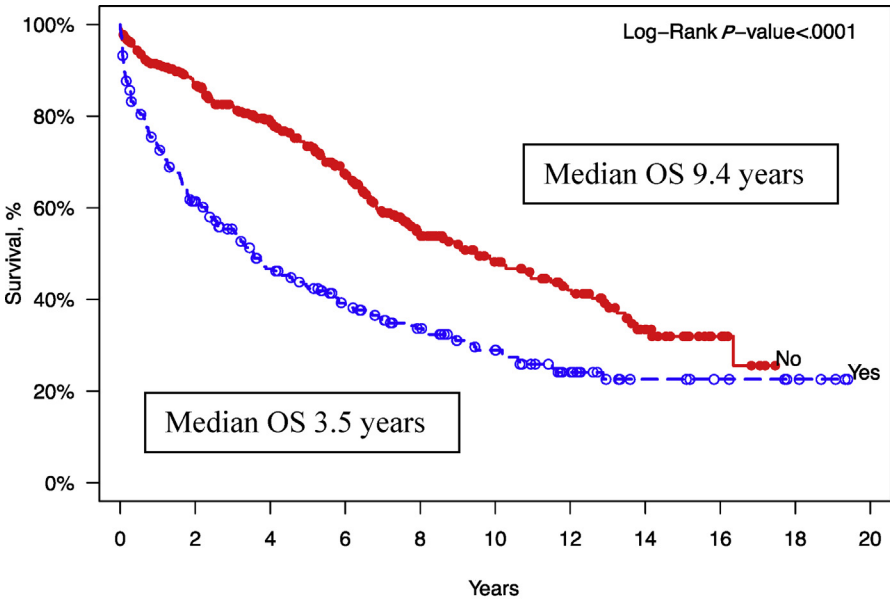
No :	307	236	159	105	61	40	22	8	3	0	0
Yes :	204	191	161	132	94	70	52	27	13	5	0

Fig. 1. OS of patients with and without hematologic CR.



287	236	194	146	92	68	48	23	9	1	0
320	194	128	93	65	43	26	12	7	4	0

Fig. 2. OS of patients with presence and absence of cardiac involvement.



356	285	222	165	102	71	50	24	8	0	0
251	145	100	74	55	40	24	11	8	5	0

Fig. 3. OS of patients with less than or equal to 2 or greater than 2 organ system involvement.

are less than 71 years old and have 1 to 2 organs involved, 1 of which must include cardiac or renal with creatinine clearance less than 51 mL/min; and (3) poor-risk patients have either 3 organs involved or advanced cardiac involvement. The cardiac biomarker staging system can also define risk of treatment-related complications while undergoing HDM-SCT.<sup>18,19</sup> Elevated cardiac troponin T levels are associated with poor survival while undergoing HDM-SCT.<sup>20</sup>

### INDUCTION REGIMENS, CHOICE, AND DURATION

Because the burden of clonal plasma cells is modest in most patients with AL amyloidosis, induction with a cytoreductive regimen before HDM-SCT, as is done in multiple myeloma, seems unnecessary, although possible benefits from infusional vincristine, adriamycin and dexamethasone (VAD) treatment before SCT have been reported.<sup>21</sup> Evidence from a randomized clinical trial indicates that the delay associated with pre-transplant cytoreduction, using oral melphalan and prednisone, can allow disease progression and can lead to survival disadvantage in patients with cardiac involvement.<sup>22</sup> Induction therapy with novel agents before HDM-SCT, specifically bortezomib and dexamethasone, is being explored in the setting of a clinical trial and data seem promising. However, induction therapy should be used with caution so that it does not cause delay of more definitive treatment or deterioration of organ function.

### STEM CELL MOBILIZATION AND COLLECTION

**Previous exposure to alkylating agents impairs hematopoietic stem cell collection.** A total dose of oral melphalan exceeding 200 mg may significantly reduce the ability to mobilize CD34+ cells. Contrary to the common experience in multiple myeloma, deaths have been reported during mobilization and leukapheresis of patients with AL amyloidosis who have cardiac or multiorgan involvement.<sup>14</sup> Overall, the incidence of major complications during stem cell mobilization and collection is approximately 15%. **To minimize the risk of toxicity, it is recommended that only granulocyte colony-stimulating factor (G-CSF) be used for mobilization because its use in combination with cyclophosphamide is associated with increased cardiac morbidity, a significantly higher number of aphereses required for CD34 harvesting, greater need of hospitalization, and increased toxicity.** However, cyclophosphamide may have a role in stem cell mobilization in patients with AL amyloidosis and multiple myeloma. The recommended dosage of G-CSF is 10 to 16 mcg/kg/d, either as a single dose or in 2 divided doses, 3 days before stem cell collection. The recommended optimal dose of CD34+ cells in AL patients is at least  $5 \times 10^6$  CD34+ cells/kg.<sup>23</sup> Contamination of the apheresis product with clonotypic plasma cells has been demonstrated but CD34 selection is not presently recommended.<sup>24</sup> Plerixafor, CXCR4 receptor antagonist, as a stem cell mobilization regimen has not been studied in subjects with AL amyloidosis in a well-designed clinical trial<sup>25</sup>; however, it can be beneficial in patients with fluid overload to reduce the dose of G-CSF, reduce the risk of capillary leak syndrome, and reduce the number of leukapheresis sessions needed for optimal stem cell collection yield.<sup>26</sup>

### CONDITIONING REGIMENS BEFORE STEM CELL TRANSPLANTATION

Total body irradiation (550 cGy) before SCT was investigated in a small feasibility study; however, it is not used in current regimens because of cardiac toxicity and what seems to be greater overall morbidity and mortality. Thus, conditioning is usually performed with intravenous melphalan alone, using a risk-adapted dose-modification

schema. Tandem cycles of HDM have shown to improve the proportion of subjects who ultimately achieve a hematologic CR in 31% of subjects, leading to overall CR rate of 67%.<sup>27</sup> A pilot study of incorporation of bortezomib with HDM in the treatment of AL amyloidosis has shown promising results with high hematologic response rates.<sup>28</sup>

### CLINICAL RESPONSES TO HIGH-DOSE MELPHALAN AND STEM CELL TRANSPLANTATION

The initial report of renal responses following HDM-SCT was published in 2001. In this report, 36% of patients had a renal response at 12 months defined as a 50% reduction in 24-hour urinary protein excretion in the absence of a 25% or greater reduction in creatinine clearance.<sup>29</sup> There was a striking difference in renal response rate among those with a complete hematologic response (71%) and those with persistence of the plasma cell dyscrasia (11%). Since then, reports of improvements in quality of life,<sup>30</sup> hepatic responses,<sup>31</sup> and cardiac responses<sup>32</sup> have been published. Similar to renal response, clinical responses in other organ systems are more evident with hematologic responses and can take up to 6 to 12 months or longer to occur.

### SPECIAL PROBLEMS ASSOCIATED WITH HIGH-DOSE MELPHALAN AND STEM CELL TRANSPLANTATION IN AL AMYLOIDOSIS

Patients with AL amyloidosis typically have organ impairment that predisposes them to increased peritransplant morbidity and mortality. Unique clinical challenges with AL amyloidosis patients that warrant special mention relate to the management of nutrition, macroglossia, orthostatic hypotension, volume status, and cardiac arrhythmias. Pretransplant assessment of gastrointestinal function and mucosal integrity is essential. The Amyloidosis Center has found that appropriate assessment includes a detailed review of gastrointestinal signs and symptoms, serial stool examinations for occult blood loss, endoscopic studies to define pathologic condition if indicated, and a complete assessment of coagulation status. Patients with poor nutrition because of gastrointestinal dysfunction and dysmotility, anorexia, or dysgeusia have generally required oral or parenteral nutrition supplements in the pretransplant and posttransplant period. Nephrotic syndrome associated with renal amyloidosis has been observed not uncommonly to lead to severe hypoalbuminemia and peripheral edema or anasarca. In patients with anasarca and serum albumin levels less than 2.0 g/dL, the Amyloidosis Center has found that albumin infusions to raise the serum albumin followed by loop diuretics are effective. Hypoalbuminemia, autonomic insufficiency, hypoadrenalism, and cardiac disease can all lead to severe orthostatic hypotension. Behavioral modifications, avoidance of dehydration, use of thigh-high fitted stockings to improve venous return, and use of midodrine (an alpha adrenergic agonist) with careful monitoring of urinary retention can be helpful in alleviation of postural hypotension from autonomic neuropathy. Cardiac disease has been observed to predispose patients to atrial and ventricular arrhythmias as well as to symptoms and signs of restrictive cardiomyopathy.<sup>33</sup> Management of such patients in coordination with an experienced cardiologist has proven to be critical. Amiodarone is often an effective antiarrhythmic, whereas beta blockers, calcium channel blockers, and digoxin have often been poorly tolerated by these patients. Deficiency of factor X, along with the poor endothelial and connective tissue integrity from amyloid deposition, is associated with an increased risk of cutaneous and mucosal bleeding, including pathognomonic raccoon-eye periorbital ecchymoses. Patients with factor X deficiency are at particularly high risk of bleeding complications during periods of

thrombocytopenia.<sup>34</sup> Hence, the Amyloidosis Center has found that screening for factor X deficiency must be done before treatment. Neither fresh frozen plasma nor cryoprecipitate are abundant sources of factor X; significant bleeding due to factor X deficiency is best treated with factor IX complex or recombinant factor VIIa. Additional unusual problems that may be encountered in these patients include difficulties with emergent endotracheal intubation in patients with macroglossia, spontaneous splenic,<sup>35</sup> esophageal and hepatic rupture,<sup>36</sup> and hypercoagulability in association with nephrotic syndrome.

#### EXPERIENCE OF HIGH-DOSE MELPHALAN AND STEM CELL TRANSPLANTATION IN THE TREATMENT OF AL AMYLOIDOSIS AT OTHER CENTERS

HDM-SCT is an effective treatment for AL amyloidosis. The results of single-center and multicenter studies are detailed in Table 1. Encouraging hematologic and clinical responses have been reported in these studies, though treatment-related mortality is substantially higher (15%–40%) than in multiple myeloma (<5%). A case-matched control study has suggested the superiority of HDM-SCT compared with conventional chemotherapy regimens<sup>37</sup>; however, the only randomized phase III study by the French group in the literature failed to show a survival benefit for HDM-SCT.<sup>38</sup> However, in this study, many of the subjects randomized to the HDM-SCT arm were not actually transplanted, the toxicity on the transplant arm was excessive, and follow-up was short. Thus, the question of optimal therapy remains open, particularly as transplant techniques are refined and nontransplant regimens are improved. However, it is clear that patients should be carefully selected for transplant because advanced cardiac disease, involvement of more than 2 organs, hypotension, and poor performance status are poor prognostic factors for the outcome of HDM-SCT.

Table 1

Results of single center and multicenter studies of high-dose melphalan and stem cell transplantation in AL amyloidosis

	Number of Patients	Treatment-Related Mortality	Hematologic CR	Organ Response
<b>Single Center</b>				
Gertz et al, <sup>49</sup> 2007	270	11%	33%	NR
Mollee et al, <sup>50</sup> 2004	20	35%	28%	Renal 46%, cardiac 25%, liver 50%
Schonland et al, <sup>51</sup> 2005	41	7%	50%	40%
Skinner et al, <sup>14</sup> 2004	277	13%	40%	44%
Chow et al, <sup>52</sup> 2005	15	0%	67%	27%
<b>Multicenter</b>				
Moreau et al, <sup>53</sup> 1998	21	43%	25%	83%
Gertz et al, <sup>54</sup> 2004	28	14%	NA	75%
Goodman et al, <sup>55</sup> 2006	92	23%	83% (CR+PR)	48%
Vesole et al, <sup>56</sup> 2006	114	18%	36%	Renal 46%, liver 58%, cardiac 47%

Abbreviations: NA, Not available; NR, Not reported; PR, Partial response.



## HIGH-DOSE MELPHALAN AND STEM CELL TRANSPLANTATION FOLLOWING HEART TRANSPLANTATION

In patients with end-stage heart failure, heart transplantation may be required as a life-saving procedure. Because of the high likelihood of amyloid recurrence in the transplanted organ, as well as progression in other organs, heart transplantation must be followed by antiplasma cell therapy. Although the long-term survival is statistically inferior to that of patients with nonamyloid heart disease, the actuarial 5-year survival seems to be 65% with treatment of the underlying plasma cell dyscrasia. Thus, carefully selected patients, without other significant organ involvement, can benefit from heart transplantation followed by aggressive antiplasma cell treatment.<sup>39–41</sup>

## SUPPORTIVE THERAPY

Supportive treatment aimed at improving or palliating organ function, maintaining quality of life, and prolonging survival while antiplasma cell therapy has time to take effect has an important impact on survival. Supportive care should be considered a fundamental part of an integrated treatment approach with these patients and requires the coordinated expertise of several specialists who are familiar with this disease. Treatment of amyloid cardiomyopathy is highly specialized because agents used for other cardiomyopathies can be dangerous in amyloidosis.<sup>42</sup> The mainstay of treatment is **salt restriction and careful administration of diuretics**, such as furosemide, scrupulously avoiding aggravation of intravascular volume contraction (due to concomitant nephrotic syndrome), and postural hypotension. If furosemide becomes ineffective in controlling edema, the addition of metolazone or spironolactone can be beneficial. Angiotensin-converting enzyme inhibitors should not be used routinely because of the high risk of precipitating hypotension in the setting of diastolic and autonomic dysfunction; however, a few patients with reduced stroke volume can benefit from these agents when used with great caution. Digoxin can be toxic because of binding to amyloid in the heart but is occasionally useful in patients with atrial fibrillation and rapid ventricular response. **Calcium channel blockers can aggravate congestive heart failure.** Patients with recurrent syncope may require permanent pacemaker implantation. Patients with ventricular arrhythmias may benefit from treatment with amiodarone or the use of artificial implantable cardiac defibrillators, though this has not been rigorously proven. In patients with end-stage heart failure, heart transplantation is the only life-saving procedure, which may allow subsequent treatment to control the amyloidogenic clone. **Orthostatic hypotension is challenging to manage. Midodrine can be helpful in some patients.** Urinary retention and piloerection are the main side effects because supine hypertension is rare in these patients. **The use of waist-high, fitted elastic stockings is helpful.** In the Amyloidosis Center experience, fludrocortisone is poorly tolerated because of aggravation of fluid retention. Continuous noradrenalin infusion has been reported to be a successful treatment of severe hypotension refractory to conventional treatment. Therapy for renal amyloidosis is limited to the control of the edema by diuretics. The main damaging mechanism is progressive tubular injury caused by glomerular protein loss. The use of angiotensin-converting enzyme inhibitors, in an attempt to reduce proteinuria, is reasonable, although their efficacy has not been proven. Treatment of hyperlipidemia should be considered. Hypercoagulable state is rarely, if ever, seen in these nephrotic patients and prophylactic anticoagulation is not recommended. End-stage renal failure is treated by dialysis. Both peritoneal dialysis and hemodialysis are equally effective. If the disease is not controlled by chemotherapy, extrarenal progression of amyloidosis is the main cause of death. **Renal transplantation should be offered on a case-by-case**

basis to patients without symptomatic extrarenal involvement.<sup>43</sup> **Diarrhea is a common problem and can be incapacitating.** Octreotide decreases diarrhea both in its short-acting form and its long-acting depository form. Chronic intestinal pseudoobstruction is usually refractory to treatment. Adequate oral or intravenous feeding is essential in patients with significant undernourishment. Patients who present with severe liver failure may be considered for liver transplantation; cases of successful sequential liver and SCTs have been reported.<sup>44</sup> **Neuropathic pain is difficult to control. Gabapentin, although well-tolerated, often fails to relieve pain. Duloxetine may be effective in controlling pain of neuropathy. Nonnephrotoxic analgesics may be used as adjuvant agents.** Bleeding in AL amyloidosis is frequent and multifactorial. Factor X deficiency can improve following effective chemotherapy, including HDM-SCT,<sup>34</sup> or after splenectomy.

### **CURRENT RECOMMENDATIONS AND FUTURE DIRECTIONS**

The data from the Amyloidosis Center and that from other centers indicate that, despite multisystem organ dysfunction, selected patients with AL amyloidosis can tolerate HDM and autologous SCT. Moreover, high-dose chemotherapy can induce complete hematologic responses in a substantial proportion of patients who complete treatment. **Furthermore, complete hematologic responses in AL amyloidosis are associated with reversal of amyloid-related organ dysfunction and may lead to prolonged survival in this disease, which is typically fatal within 2 years when managed with standard oral chemotherapy regimens of oral cyclic melphalan and prednisone.**

During the past 20 years, a large number of AL amyloidosis patients with HDM-SCT have been treated, including patients older than 65 years old,<sup>45</sup> patients on dialysis,<sup>46</sup> and patients with cardiac disease.<sup>47,48</sup> Although patient selection remains important in achieving an acceptable outcome, the author believes it is in part attributable to the multidisciplinary approach to patient management. A team of subspecialists who are familiar with the manifestations and treatment of amyloidosis evaluate each patient. These subspecialists remain available to the transplant physicians throughout therapy and the amyloid clinical team meets regularly to review each patient's progress during treatment. **The Amyloidosis Center encourages other transplant centers undertaking treatment of these complicated patients to adopt a similar multidisciplinary management approach.**

### **SUMMARY**

**Promising treatments,** other than HDM-SCT, are available for patients with AL amyloidosis. Although these treatment regimens are not discussed here, the availability of new regimens for treatment of AL amyloidosis may, in the future, provide additional options for patients who are not eligible for HDM-SCT. Timing and sequencing of regimens containing these agents, and comparison with or combination with HDM-SCT, will be determined in future trials.

**Prompt diagnosis of amyloidosis and appropriate referral has great potential to improve outcome** for these patients. AL amyloidosis should be considered in the differential diagnosis of patients being evaluated for a variety of syndromes, including nephrotic range proteinuria, unexplained nonischemic cardiomyopathy, nondiabetic peripheral or autonomic neuropathy, and unexplained hepatomegaly. It is essential to recognize AL amyloidosis as the cause of macroglossia and periorbital echymoses. All patients presenting with monoclonal gammopathy or smoldering myeloma should be screened for nephropathy and cardiomyopathy on presentation and periodically afterward. Despite improvements in the diagnosis and treatment of AL

amyloidosis, continued basic and clinical research is needed to continue to improve the outcome for these patients.

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