High-Dose Melphalan and Autologous Stem-Cell Transplantation in Patients with AL Amyloidosis: An 8-Year Study

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Background: **AL amyloidosis is a fatal disease resulting from tissue deposition of amyloid fibrils derived from monoclonal immunoglobulin light chains. Treatment with oral chemotherapy is minimally effective.**

Objective: **To test survival and organ response in a large sample of patients treated with high-dose intravenous melphalan (100 to 200 mg/m^2) and autologous blood stem-cell transplantation.**

Design: **8-year longitudinal analysis of clinical effectiveness.**

Setting: **University-affiliated specialty referral clinic.**

Patients: **701 consecutive new patients with AL amyloidosis.**

Intervention: **High-dose chemotherapy and autologous stem-cell transplantation for patients who met eligibility requirements based on organ involvement and clinical status.**

Measurements: **Survival analysis of all patients evaluated and a detailed analysis of treatment outcome in the subgroup that received high-dose melphalan and stem-cell transplantation.**

Results: **Among 701 patients with AL amyloidosis, 394 (56%) were eligible for high-dose melphalan and stem-cell transplantation; 82 did not proceed with treatment because of patient choice or disease progression. Median survival of the 312 patients who initiated treatment was 4.6 years. A complete hematologic response, defined as no evidence of an underlying plasma cell dyscrasia 1 year after treatment, was achieved in 40% of patients and was associated with prolonged survival. Statistically significant improvements occurred in end-organ disease and were greater in patients with a complete hematologic response. Mortality rate within 100 days of treatment with high-dose melphalan and stem-cell transplantation was 13%; patients with cardiomyopathy had the highest mortality rates.**

Conclusions: **Treatment of selected patients with AL amyloidosis by using high-dose melphalan and stem-cell transplantation resulted in hematologic remission, improved 5-year survival, and reversal of amyloid-related disease in a substantial proportion.**

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The most common form of systemic amyloidosis in the United States is AL (or primary) amyloidosis. In this disease, amyloid fibrils are derived from monoclonal immunoglobulin light chains that are produced by an underlying clonal plasma cell dyscrasia. Although the burden of plasma cells is generally low, accumulation of amyloid deposits in vital organs leads to progressive disability and death. The median survival of untreated patients after diagnosis is 12 months and less than 5 months for those with cardiomyopathy (1–5). AL amyloidosis is reported to occur in 5 to 12 persons per million per year in the United States; however, death records and autopsy results suggest that the incidence may be higher (6, 7). Treatment with oral melphalan results in a modest increase in median survival but rarely eliminates the plasma cell dyscrasia and is not effective for rapidly progressive disease (8–10). Alternative chemotherapy regimens have not improved survival further (11–15).

Promising treatment outcomes observed with high-dose intravenous melphalan and autologous stem-cell transplantation in multiple myeloma (16–19) provided a rationale for testing the hypothesis that this treatment would improve survival for patients with AL amyloidosis. Favorable responses to high-dose melphalan and stem-cell transplantation in patients with AL amyloidosis have been reported in case reports and in small series; however, treatment-related mortality was high in multicenter trials (20–28). Our initial experience with treatment in AL amyloidosis indicated that selected patients can tolerate treatment and that hematologic responses and reversal of amyloid-related organ dysfunction can be achieved (29–32). Since 1994, we have evaluated 701 patients with AL amyloidosis, 312 of whom initiated high-dose melphalan treatment and stem-cell transplantation. This longitudinal study examines survival, hematologic response, and improvement of amyloid-related organ disease in patients who were treated with high-dose melphalan and stem-cell transplantation. We contrast these data with features and survival of a simultaneous cohort of patients who were not eligible for treatment.

METHODS

Patients

Between July 1994 and June 2002, 701 consecutive patients with AL amyloidosis were evaluated and clinical data were collected with the approval of the Institutional Review Board of Boston University Medical Center. All patients had biopsy-proven amyloid disease and a documented plasma cell dyscrasia, which was diagnosed by the presence of clonal plasma cells in the bone marrow or a monoclonal gammopathy detected by immunofixation electrophoresis of serum or urine proteins (**Figure 1**). To exclude another type of systemic amyloidosis and a monoclonal gammopathy of unknown significance, all patients with findings compatible with familial or secondary (AA)

Context

AL amyloidosis responds poorly to oral chemotherapy and rarely leads to elimination of plasma cell dyscrasia. Amyloid cardiomyopathy is a particularly fatal complication of the disease.

Contribution

Analysis of consecutive patients with AL amyloidosis from 6 separate trials over 8 years shows that high-dose intravenous melphalan therapy combined with autologous stem-cell transplantation greatly improves duration of survival and ameliorates organ dysfunction.

Implications

Intravenous melphalan therapy combined with stem-cell transplantation represents a clinically significant improvement in treating AL amyloidosis and shows promise in reversing amyloid cardiomyopathy.

–The Editors

amyloidosis were tested by DNA analysis for gene mutations in transthyretin, apolipoprotein A1, fibrinogen, and lysozyme known to be associated with amyloidosis and by immunohistochemistry of the biopsy tissue for AA amyloid fibril deposits (33). Patients with multiple myeloma (bone marrow plasmacytosis ≥30% or lytic bone lesions) were excluded. In patients older than 70 years of age with cardiomyopathy only, a diagnosis of senile cardiac amyloidosis (caused by wild-type transthyretin) was excluded by immunohistochemical examination of a tissue biopsy specimen using antiserum to transthyretin. All patients were evaluated for degree of organ involvement by physical examination, standardized blood tests, electrocardiography, echocardiography, chest radiography, pulmonary function tests, and a 24-hour urine collection. All patients were evaluated by a hematologist and cardiologist and, when appropriate, by nephrology, pulmonology, gastroenterology, and neurology specialists.

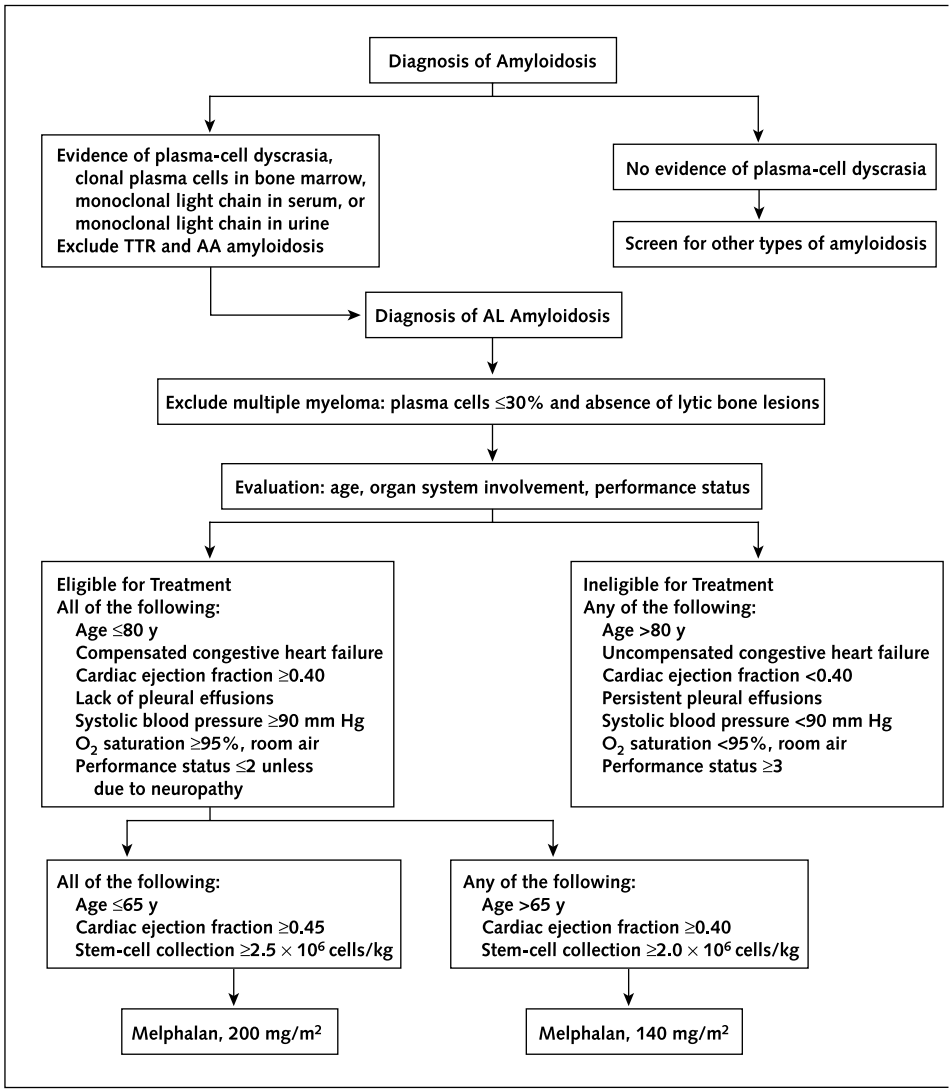
High-Dose Melphalan and Stem-Cell Transplantation Eligibility and Protocols

Patients were enrolled in several sequential institutional review board–approved protocols during the 8-year study period. Eligibility criteria for all protocols required biopsy-proven amyloid disease; evidence of a plasma cell dyscrasia; at least 1 major organ affected by amyloid disease; and minimum measures of cardiac, pulmonary, and performance status (**Figure 1**). Functional measures included cardiac ejection fraction 0.4 or greater, absence of symptomatic pleural effusions, absence of heart failure or arrhythmia resistant to medical management, oxygen saturation of 95% or greater on room air, lung diffusing capacity of 50% or more of predicted, supine systolic blood pressure of 90 mm Hg or greater, and Southwest Oncology Group performance status score of 2 or less unless limited by neuropathy (on a scale of 0 to 4, reflecting percentage of the day [0%, 25%, 50%, 75%, or 100%] spent in bed or in a chair). Minor variations in eligibility requirements for age, renal function, amount of previous chemotherapy, and time from diagnosis while on some protocols are noted in the following discussion; the number of patients affected is also given.

The first protocol (July 1994 to December 1995) enrolled 13 patients 60 years of age or younger with serum creatinine values of 176.8 μmol/L (2.0 mg/dL) or less; these patients were treated with melphalan, 200 mg/m^2 (29). Subsequent protocols had no restriction for impaired renal function. A second protocol (April 1995 to October 1996) enrolled 28 patients 70 years of age or younger and used a lower dose of melphalan, 100 mg/m^2 (31). Two protocols (January 1996 to June 1998) evaluated the use of CD34$^+$-selected stem cells in 16 patients (34). The fifth protocol (October 1996 to September 2000) randomly assigned 100 previously untreated patients to treatment with high-dose melphalan and stem-cell transplantation immediately or after 2 cycles of oral melphalan and prednisone. There was no age limit for this protocol; however, melphalan, 140 mg/m^2, was given to patients who were older than 65 years of age or had a cardiac ejection fraction between 0.40 and 0.44. The sixth protocol (November 2000 to the present) has enrolled 29 patients 65 years of age or younger. On this protocol, enough stem cells are collected initially to give a second cycle of chemotherapy within the first year if a complete response has not been achieved after an initial course of melphalan at a dose of 200 mg/m^2. Other patients who met eligibility criteria (August 1996 to the present) but were excluded from an active protocol because of previous treatment or time from diagnosis were treated by using the established dosing guidelines. Patients who did not meet eligibility for treatment with high-dose melphalan and stem-cell transplantation were grouped according to reasons for ineligibility and were analyzed for survival.

Organ system involvement was defined by physical examination; postural blood pressure determinations; standardized serologic laboratory measurements of kidney, liver, and endocrine function; coagulation studies, including factor X levels; electrocardiography; echocardiography; chest radiography; pulmonary function tests with walking oximetry; and a 24-hour urine collection for protein excretion. Cardiac involvement was defined by septal or posterior wall thickening of 13 mm or greater on echocardiography or a clinical syndrome of congestive heart failure or cardiac arrhythmia in the absence of preexisting cardiac disease. Renal involvement was diagnosed by proteinuria of 500 mg/24 h or greater or an elevated serum creatinine concentration in the absence of other causes of renal disease. Gastrointestinal involvement was diagnosed by involuntary loss of 10% of body weight, unexplained diarrhea, hepatomegaly of 4 cm or more below the right costal margin on physical examination, or alkaline phosphatase level

Figure 1. **Algorithm for patient selection and treatment with high-dose melphalan and stem-cell transplantation.**



2 or more times the upper limit of normal values. Peripheral neuropathy was diagnosed by symptoms and physical examination or nerve conduction studies, and autonomic neuropathy was defined by orthostatic hypotension—a decrease in systolic blood pressure of 20 mm Hg or greater with upright posture in euvolemic patients. Soft tissue involvement was diagnosed by clinical evidence of macroglossia, soft tissue or subcutaneous deposits, amyloid arthropathy, lymphadenopathy, or nail dystrophy. Coagulation factor X level was considered deficient if it was 50% or less of normal.

Stem-Cell Collection and High-Dose Chemotherapy

Peripheral blood stem cells were collected by leukapheresis after mobilization using granulocyte colony-stimulating factor. A minimum yield of 2.0×10^6 $CD34^+$cells/kg of body weight was required to support high-dose chemotherapy. The patient's age and cardiac status and the number of stem cells collected determined the melphalan dose (**Figure 1**). A dose of 200 mg/m^2 was administered to patients who were 65 years of age or younger and who had a cardiac ejection fraction of 0.45 or greater and a stem-cell collection of at least 2.5×10^6 $CD34^+$cells/kg. A dose of 140 mg/m^2 was administered to patients who were older than 65 years of age, who had a cardiac ejection fraction of 0.4 to 0.44, or who had a stem-cell collection of 2.0 to 2.5×10^6 $CD34^+$cells/kg. The melphalan dose was divided over 2 consecutive days. Stem-cell infusions (day 0) were performed 24 to 72 hours after the last dose of melphalan. No maintenance therapy was given to patients after high-dose melphalan treatment and stem-cell transplantation.

Measurements of Response after Treatment with High-Dose Melphalan and Stem-Cell Transplantation

Hematologic and end-organ responses to treatment were evaluated annually. A complete hematologic response required no bone marrow evidence of clonal plasma cells

Table 1. **Comparison of the Clinical Features of Patients with AL Amyloidosis according to Eligibility Status for Treatment with High-Dose Melphalan and Stem-Cell Transplantation***

Feature	Eligible Patients (n = 394)	Ineligible Patients (n = 307)	P Value
Age, *y*	56.9 ± 10.3	64.6 ± 10.2	<0.001
Women, %	41.1	40.1	>0.2
Time from first symptom to diagnosis, *mo*	12.5 ± 18.9	15.4 ± 22.7	0.078
Time from diagnosis to referral, *mo*	6.8 ± 16.3	10.5 ± 21.0	0.014
Clinical findings			
Organ systems involved (of the 5 listed below), *n*	2.5 ± 1.2	2.9 ± 1.2	<0.001
Performance status	1.1 ± 0.8	1.9 ± 0.9	<0.001
Weight loss, %	45.4	58.0	<0.001
Free light chain in serum, %	68.5	70.7	>0.2
κ light chain, %	16.0	25.7	0.002
Organ involvement, %			
Heart	43.4	65.8	<0.001
Kidney	85.8	73.3	<0.001
Gastrointestinal and liver	56.4	70.0	<0.001
Neuropathy	48.2	57.3	0.017
Soft tissue	20.0	27.4	0.023

*Values presented with plus/minus signs are means ± SD.

by immunohistochemical staining or monoclonal gammopathy, as detected by immunofixation electrophoresis of serum and urine proteins at 1 year after treatment. Evidence of a persistent clonal plasma cell disorder was termed a *noncomplete response*.

Clinical responses were measured at 1 year and were defined as follows. A cardiac response occurred if the intraventricular septal thickness was abnormal on echocardiography before treatment and decreased by 2 mm or more or if symptoms of congestive heart failure improved, defined as a decrease of at least 1 grade in New York Heart Association class without an increase in diuretic dose. A renal response occurred if 24-hour urine protein excretion of 1 g or more declined by at least 50% and creatinine clearance was reduced by 25% or less. A gastrointestinal response occurred if hepatomegaly decreased by 2 cm or more on physical examination, if an elevated alkaline phosphatase level decreased by 50% or more, or if pretreatment symptoms of diarrhea disappeared and weight loss stabilized or reversed. A peripheral neuropathy response was defined as improvement in sensory neuropathy on serial examinations by 1 neurologist and resolution of preexisting orthostatic hypotension defined an autonomic neuropathic response. A factor X response was defined as normalization of the factor X level. A performance status response was defined as an improvement of 1 or more in the performance measure.

Statistical Analysis

Clinical and demographic factors were compared among subgroups by using *t*-tests for continuously measured variables and the chi-square test for dichotomous variables. Logistic regression that included all clinical factors (age, sex, time from first symptom to diagnosis and from diagnosis to referral, each organ involvement individually, total number of organs involved, performance status, weight loss, presence of a free light chain in serum, and clonal light chain type) was used to determine quintiles of the propensity to use the maximum dose of melphalan (200 mg/m^2). The fit of this model was assessed by using the c-statistic. These propensity quintiles were taken into account (defining 4 dummy variables) before determining, in a stepwise proportional hazards regression, whether melphalan dose related to survival after treatment with high-dose melphalan and stem-cell transplantation (35).

Kaplan–Meier survival plots were used to display survival distributions. Five-year survival rates were estimated by the actuarial (life-table) method and compared by using the z-test. Differences between survival distributions for subgroups were characterized by using hazard ratios. The likelihood ratio test was used to test the significance of unadjusted and adjusted hazard ratios. The effect of light chain clonal type (κ vs. λ), the presence of free light chain in the serum, or melphalan dose on the probability of a complete hematologic response was tested by logistic regression. The results are presented in a tabulation of proportions of patients with a complete hematologic response for combinations of each of these 3 variables. Analyses were conducted by using SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Sources

The funding sources had no role in the design, conduct, and reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Patient Sample

Fifty-six percent (394 of 701) of all new patients with AL amyloidosis met eligibility criteria for high-dose melphalan treatment and stem-cell transplantation; 44% (307

of 701) were ineligible. Forty-one percent of all patients were women, and there were no sex differences among the patient groups. Of the 394 eligible patients, 63 declined treatment and 19 became ineligible before treatment because of disease progression. Stem-cell mobilization was initiated in 312 patients; 35 patients did not proceed to high-dose melphalan treatment and stem-cell transplantation because of death ($n = 13$) or complications of the mobilization regimen ($n = 22$).

Clinical features that distinguished patients eligible for high-dose melphalan treatment and stem-cell transplantation from those who were ineligible included younger age, shorter time from diagnosis to referral, better performance status, and less organ involvement (**Table 1**). Cardiac, gastrointestinal and liver, neuropathy, and soft-tissue involvement, as well as weight loss and a κ light chain plasma cell dyscrasia, were less frequent among eligible patients, whereas renal involvement was more frequent. Half of the 394 eligible patients had 3 or more organs involved ($n = 196$), and 30% of the eligible patients had 2 organs involved ($n = 118$). Only 20% of eligible patients had a single organ involved ($n = 80$); of these, 60 patients had renal disease only. Survival, hematologic response, and organ improvement data were available on all patients; no patient was lost to follow-up.

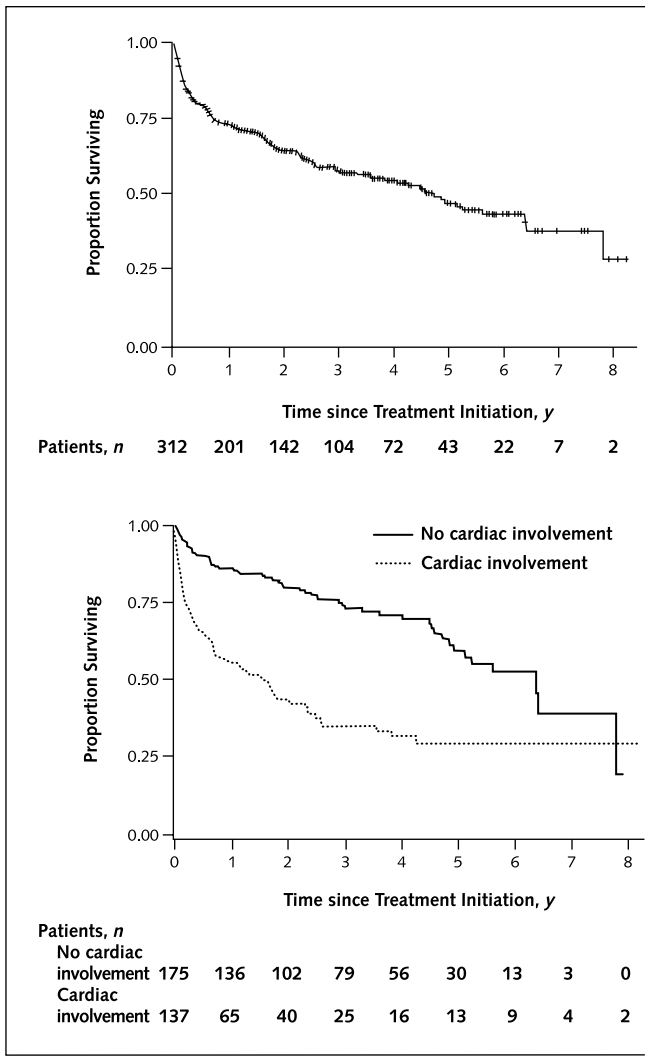
Survival

The median survival of all 312 patients who began the stem-cell mobilization regimen was 4.6 years; 56% of patients (174 of 312) remain alive, and the estimated 5-year survival rate is 47% (95% CI, 39% to 54%) (**Figure 2**). For the 137 patients with cardiac involvement, median survival from the start of the mobilization regimen was 1.6 years; 40% of patients (55 of 137) are still alive, and the estimated 5-year survival rate is 29% (CI, 19% to 39%) (**Figure 2**). In contrast, median survival for the 175 patients without cardiac involvement was 6.4 years. Their estimated 5-year survival rate is 60% (CI, 50% to 72%) ($P < 0.001$), and 68% (117 of 173) are still alive. Nineteen percent of patients (60 of 312) were 65 years of age or older, and their median survival of 4.9 years was equivalent to the 4.6-year survival of younger patients ($P > 0.2$).

Mortality and Morbidity

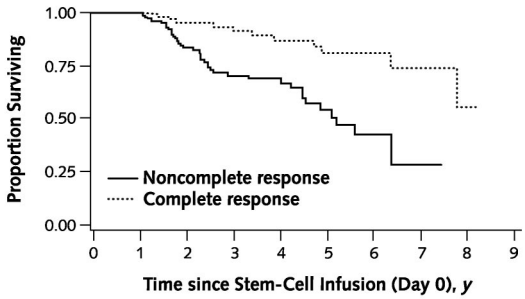
Of the 277 patients who completed treatment with high-dose melphalan and stem-cell transplantation, 36 (13%) died of treatment-related causes (≤100 days after day 0). Fifteen deaths were cardiac-related, 9 were due to sudden death or arrhythmia, and 6 were due to heart failure. Sepsis was the cause of death in 9 patients. Between 100 days and 1 year, 21 patients died; 11 of these deaths were cardiac-related, 5 were due to sudden death or arrhythmia, and 6 were due to heart failure. Morbidity during the post-transplantation period included opportunistic infections in 31 patients: pneumocystic pneumonia in 4 patients, herpes zoster in 26 patients, and cytomegalovirus infection in 1 patient. Other serious complications that occurred in the post-transplantation period included gastrointestinal bleeding that required transfusion in 26 patients, renal failure that required dialysis in 14 patients, and spontaneous rupture of the spleen in 2 patients. No nonhematologic late toxicities were observed. Two patients who had been treated with 600 mg or more of oral melphalan before high-dose melphalan and stem-cell transplantation died at 2 and 5 years after treatment as a result of secondary acute myelogenous leukemia, and another patient remained pancytopenic and transfusion dependent for a prolonged period after transplantation.

Figure 2. **Survival curve for all patients (*top*) and for patients with cardiac versus noncardiac involvement (*bottom*).**



The top panel shows survival for all 312 patients who initiated treatment with high-dose melphalan and stem-cell transplantation. Median survival is 4.6 years, and vertical lines indicate patients who are still alive. The bottom panel shows survival for 137 of 312 patients treated with high-dose melphalan and stem-cell transplantation who had cardiac involvement and for 175 of 312 patients treated with high-dose melphalan and stem-cell transplantation who did not have cardiac involvement. The median survival for patients with cardiac involvement was 1.6 years, and the median survival for patients who did not have cardiac involvement was 6.4 years ($P < 0.001$).

Figure 3. **Survival curves according to hematologic response at 1 year from treatment.**



Patients, *n*									
Complete response	73	73	61	49	35	24	16	6	2
Noncomplete response	108	108	77	50	32	17	4	1	0

One hundred eighty-one patients were evaluable for hematologic response at 1 year after treatment. Survival is shown for 73 of 181 patients with a complete hematologic response and for 108 of 181 patients with a noncomplete response. The median survival cannot be determined for the complete response group because 85% of those patients are still alive; the median survival for the noncomplete response group is 5.2 years ($P = 0.001$).

Factors Predicting Survival

Among the 277 patients who completed treatment, 155 received a melphalan dose of 200 mg/m^2 and had a median survival of 7.8 years; 72% (111 of 155) of these patients are still alive, and the 5-year survival rate is 61% (CI, 50% to 72%). Modified high-dose melphalan (100 or 140 mg/m^2) was given to 122 patients. These patients had a median survival of 2.9 years; 48% (59 of 122) are still alive, and the 5-year survival rate is 41% (CI, 30% to 51%) ($P < 0.001$).

While the decision to administer the higher dose was made prospectively according to the treatment protocols (primarily on the basis of age and cardiac status), other factors were found retrospectively that correlated with dose selection. In a model that included all factors in **Table 1**, the statistically significant factors that were associated with reduced dose were older age, worse performance status, and longer time from diagnosis to referral. The c-statistic for this model was 0.814, which indicated good prediction (data not shown). After adjusting for propensity quintile and for the clinical factors in **Table 1**, we found that improved survival was associated with the higher dose of melphalan (hazard ratio, 0.51 [CI, 0.32 to 0.79]).

Hematologic Response

The hematologic response was evaluated 1 year after treatment. Fifty-seven patients died before the 1-year follow-up visit, and 1 year has not passed since treatment for 39 patients. Of the 181 evaluable patients, 40% (73 of 181) achieved a complete hematologic response, that is, they had no evidence of a persistent plasma cell dyscrasia in the bone marrow or of monoclonal gammopathy in serum or urine. Among the 60 patients age 65 years and older who survived and were evaluable, the complete hematologic response rate did not differ from that of younger patients ($P = 0.182$). Of the patients with a complete response at 1 year, 8% (6 of 73) were found to have had a relapse at 2 years. Later relapses have not been seen.

A statistically significant survival advantage was noted for patients who achieved a complete hematologic response (**Figure 3**). The estimated 5-year survival rate from day 0 was 82% (CI, 71% to 93%). The median survival could not be calculated and probably will exceed 8 years; 85% (62 of 73) of patients with a complete hematologic response survive. By comparison, the estimated 5-year survival rate for patients who did not have a complete hematologic response was 55% (CI, 42% to 68%). Their median survival was 5.2 years, and 65% (70 of 108) survive ($P < 0.001$). Nearly all patients who did not achieve a complete hematologic response had evidence of a partial hematologic response.

Factors Predicting Complete Hematologic Response

A complete hematologic response was positively associated with the dose of melphalan and κ light chain clonal disease, whereas the detection of free light chains in serum was associated with a decreased likelihood of a complete hematologic response. **Table 2** shows the proportion of patients who experienced hematologic response, according to clonal light chain type, presence or absence of a free light chain in the serum, and the dose of melphalan. Some combinations of these factors are uncommon, but it is clear that the higher dose of melphalan improved the likelihood of a complete hematologic response when a free light chain was in the serum.

Clinical Response

Changes in organ function and performance status were measured at 1 year and correlated with hematologic responses (**Table 3**). Improvement in at least 1 organ occurred in 66% of patients (48 of 73) with a complete hematologic response and in 30% of patients (32 of 108) who did not have a complete hematologic response ($P < 0.001$). Objective measures of improvement were available for cardiac, renal, gastrointestinal and liver, and neurologic

Table 2. **Effect of Melphalan Dose on the Probability of a Complete Response for All Light Chain Combinations Associated with AL Amyloidosis in 181 Patients**

κ Light Chain	Serum Free Light Chain	Dose Associated with Complete Hematologic Response	
		100–140 mg/m^2	200 mg/m^2
		n/n (%)	
No	No	9/22 (41)	17/29 (59)
No	Yes	6/34 (18)	23/69 (33)
Yes	No	3/3 (100)	10/11 (91)
Yes	Yes	4/9 (44)	1/4 (25)
Total		22/68 (33)	51/113 (45)

Table 3. **Organ Improvement at 1 Year according to Hematologic Response in 181 Patients**

Organ System	Improvement in Patients with Complete Hematologic Response (n = 73)*	Improvement in Patients with Noncomplete Hematologic Response (n = 108)*	*P* Value
	% (n/n)		
Cardiac	27 (6/22)	17 (6/36)	>0.2
Renal	63 (29/46)	11 (7/68)	<0.001
Gastrointestinal and liver	57 (26/46)	30 (13/44)	0.010
Neuropathy	47 (17/36)	29 (13/45)	0.090
Soft tissue	11 (1/9)	0 (0/17)	0.161
Performance status ≥1	53 (38/72)	22 (23/106)	<0.001
Factor X	40 (2/5)	38 (3/8)	>0.2
Patients with 1 or more improvement†	66 (48/73)	30 (32/108)	<0.001

* n/n = number improved/number involved at baseline.
† Improvement relates to 5 organ systems: cardiac, renal, gastrointestinal and liver, neuropathy, and soft tissue.

involvement and occurred as follows: a decrease of 2 mm or more in a thickened intraventricular septum in 10 patients with cardiac involvement, a 50% or greater decrease in proteinuria without reducing creatinine clearance in 36 patients with renal involvement, a 2 cm or greater decrease in 17 patients with an enlarged liver, a 50% or greater decrease in elevated alkaline phosphatase level in 6 patients with gastrointestinal and liver involvement, and a resolution of orthostatic hypotension in 21 patients with autonomic neuropathy. Subsequent follow-up showed further improvements in organ disease after 1 year.

Patients Ineligible for Treatment with High-Dose Melphalan and Stem-Cell Transplantation

Forty-four percent of the patients (307 of 701) were considered ineligible for treatment with high-dose melphalan and stem-cell transplantation at initial evaluation because of impaired organ function or poor performance status (n = 224), age (n = 31), extensive previous chemotherapy (n = 13), or absence of visceral organ involvement (n = 39). Those patients with impaired organ function or poor performance status made up most (73% [224 of 307]) of the ineligible group. Their median survival from evaluation was 4 months, and only 16% (35 of 225) of this group remain alive.

Discussion

This study examined 701 consecutive patients with AL amyloidosis who were referred to a specialty amyloid clinic during an 8-year period. Of necessity, patients treated with high-dose melphalan and stem-cell transplantation represent a selected sample, yet we found that more than half of the referral sample (394 of 701) were eligible for treatment. Reasons patients did not meet relatively liberal eligibility criteria were most often related to severely impaired major organ function, a finding that was significantly less frequent among patients referred early after diagnosis. The survival, hematologic response, and organ system improvements of the patients who completed treatment with high-dose melphalan and stem-cell transplantation were substantially greater than those reported for any other therapy (8–11).

The analysis of the clinical data in this large series contrasts with other reports on treatment selection bias, survival of patients older than 65 years of age who were treated with high-dose melphalan and stem-cell transplantation, and survival with respect to number of organs involved. Selection bias was suggested by a recent retrospective study concluding that eligibility for high-dose melphalan treatment and stem-cell transplantation in and of itself predicted prolonged survival (36): A group of patients, defined retrospectively as transplant eligible according to relatively restrictive criteria but treated with oral therapies, was found to have a 5-year survival rate of 36% (CI, 30% to 43%). However, this was significantly exceeded by the 5-year survival rate (52% [CI, 46% to 58%]; z = 3.45; P = 0.002) of all 312 patients who initiated treatment with high-dose melphalan and stem-cell transplantation in our study.

Another study has suggested that patients 65 years of age or older should not be considered for treatment with high-dose melphalan and stem-cell transplantation (26). We treated otherwise eligible patients up to age 80 years and found no difference in survival for patients age 65 years or older compared with younger patients.

We found that the survival of patients treated with high-dose melphalan and stem-cell transplantation was adversely affected by the presence of cardiac involvement at the time of patient evaluation. A positive effect on survival was identified with the higher dose (200 mg/m^2) of melphalan. Other clinical factors may also be important, but because of their use in the propensity score for determining the dose of melphalan, an estimate of their effect on survival would be confounded.

The positive influence of κ light chain clonal disease on the likelihood of complete hematologic response (**Table 2**) remains unexplained. We advise caution in interpreting the presence of a κ light chain as favorable since, as shown

in **Table 1**, patients with a κ light chain represent a higher proportion of patients ineligible for treatment.

A complete hematologic response was achieved by 40% of patients, and these responses were durable with few relapses. This confirms data reported in other small series showing that treatment with high-dose melphalan and stem-cell transplantation results in a superior hematologic response compared with any other therapy. Evidence of clinical organ improvement and reversal of amyloid-related disease occurred in 44% of the patients evaluated 1 year after high-dose melphalan treatment and stem-cell transplantation, and those who achieved complete hematologic response were more likely to improve than those who did not (66% vs. 30%, respectively). Organ improvement has rarely been seen before in patients with this rapidly fatal disease. Our previous reports on improvements in renal function and factor X deficiency in patients treated with high-dose melphalan and stem-cell transplantation corroborate these findings (37, 38). Survival benefit and clinical improvement in organ function extended to patients who did not achieve a complete hematologic response.

In conclusion, AL amyloidosis is a complex disease in which patients have clinical features of progressive amyloid-related organ disease associated with a plasma cell dyscrasia. This study demonstrates that patients who meet appropriate treatment eligibility criteria at the time of initial evaluation can tolerate treatment with high-dose melphalan and stem-cell transplantation managed in a multidisciplinary fashion. The treatment prolongs survival, reverses hematologic and amyloid-related organ disease, and seems to be superior to other forms of chemotherapy that have been studied. Patient age, number of organs involved with amyloid disease, and renal function do not limit the treatment benefits. These data suggest that treatment with high-dose melphalan and stem-cell transplantation should be considered early in the course of disease for eligible patients with AL amyloidosis.

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