

Amyloidosis

High-dose intravenous melphalan and autologous stem cell transplantation as initial therapy or following two cycles of oral chemotherapy for the treatment of AL amyloidosis: results of a prospective randomized trial

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Summary:

A prospective randomized trial was conducted to study the timing of high-dose intravenous melphalan and autologous stem cell transplantation (HDM/SCT) in AL amyloidosis. In all, 100 newly diagnosed patients were randomized to receive HDM/SCT, either as initial therapy (Arm-1) or following two cycles of oral melphalan and prednisone (Arm-2). The objectives of the trial were to compare survival and hematologic and clinical responses. With a median follow-up of 45 months (range 24–70), the overall survival was not significantly different between the two treatment arms ($P = 0.39$). The hematologic response and organ system improvements after treatment did not differ between the two groups. Fewer patients received HDM/SCT in Arm-2 because of disease progression during the oral chemotherapy phase of the study, rendering them ineligible for subsequent high-dose therapy. This affected patients with cardiac involvement particularly, and led to a trend for an early survival disadvantage in Arm-2. Hence, newly diagnosed patients with AL amyloidosis eligible for HDM/SCT did not benefit from initial treatment with oral melphalan and prednisone, and there was a survival disadvantage for patients with cardiac involvement if HDM/SCT was delayed by initial oral chemotherapy.

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AL (or ‘primary’) amyloidosis is the most common form of systemic amyloidosis. In this lethal disease, fibrillar amyloid protein deposits are derived from immunoglobulin light chains produced by an underlying clonal plasma cell dyscrasia. Although the burden of clonal plasma cells is generally low in AL amyloidosis, accumulation of amyloid deposits in the kidneys, heart, liver, and autonomic nervous system leads to progressive disability, organ failure, and death.^{1–5} The median survival of untreated patients is 10–14 months from the time of diagnosis overall, and less than 5 months for patients with cardiomyopathy and congestive heart failure (CHF).^{6,7} AL amyloidosis is reported to occur in 5–12 persons per million per year in the United States; however, death records and autopsy results suggest that the actual incidence is higher.^{1,2}

Several studies have shown that treatment with cyclic oral melphalan and prednisone slows disease progression in some patients and results in a modest increase in median survival to 17 months from the time of diagnosis.^{8–10} However, this treatment only rarely results in complete hematologic remissions (ie elimination of the underlying plasma cell dyscrasia), and is of little benefit for most patients with rapidly progressive disease. Nevertheless, it has become the standard treatment offered to patients, and alternative combination chemotherapy regimens have not been shown to prolong survival beyond that observed with oral melphalan and prednisone.^{11–14}

High-dose intravenous melphalan and autologous stem cell transplantation (HDM/SCT) has become a first-line treatment for patients with multiple myeloma, because of high hematologic response rates and survival benefits when compared with conventional chemotherapy regimens.^{15–18} Promising treatment outcomes observed with HDM/SCT in myeloma provided a rationale for evaluating this aggressive treatment approach in AL amyloidosis. HDM/SCT has been shown to induce both hematologic and clinical remissions in AL amyloidosis, and it appears to prolong survival substantially when hematologic remissions are achieved.^{19–26} However, HDM/SCT is a high-risk form of treatment for AL amyloidosis because of the multi-system involvement and organ dysfunction characteristic of this disease,^{27–29} and is generally carried out at specialized referral centers.

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Treatment of multiple myeloma with HDM/SCT is commonly preceded by several cycles of VAD chemotherapy to reduce the bone marrow plasma cell burden prior to stem cell collection and high-dose melphalan treatment.^{15–18} However, VAD has side effects for patients who have cardiac, renal, and/or neurologic disease that are common in most patients with AL amyloidosis. In fact, in one published study designed to use VAD prior to HDM/SCT, only one of 12 patients actually received the VAD regimen.³⁰ Oral melphalan and prednisone, however, is well tolerated and is the most common regimen that patients with AL amyloidosis receive prior to referral to a transplant center or while awaiting high-dose treatment. It is plausible that such therapy would partially suppress the clonal plasma cell disorder or stabilize the clinical disease, and enhance eventual responses to HDM/SCT. On the other hand, oral chemotherapy could potentially interfere with stem cell collection, delay more definitive therapy, or increase the toxicity of high-dose chemotherapy.

We, therefore, conducted a prospective, randomized trial to study the optimal timing of high-dose melphalan and autologous stem cell transplantation in the treatment of AL amyloidosis. The specific objectives of this trial were to determine whether an initial course of oral cyclic melphalan and prednisone prior to high-dose melphalan and stem cell transplant would be advantageous or disadvantageous with respect to eventual hematologic responses and survival of patients with AL amyloidosis, who were newly diagnosed and had no prior chemotherapy.

Methods

Patients

Between October 1996 and September 2000, 100 patients with AL amyloidosis were enrolled on this randomized trial, approved by the institutional review board of Boston University Medical Center. All patients had biopsy-proven amyloid disease and a documented plasma cell dyscrasia, indicated by clonal plasma cells in the bone marrow and/or by detection of a monoclonal gammopathy by immunofixation electrophoresis of serum and urine proteins. Patients who met the diagnostic criteria for multiple myeloma, bone marrow plasmacytosis of >30%, Bence Jones proteinuria >1 g/day and/or skeletal lytic lesions, were excluded from the trial. All patients were evaluated for the extent of organ system involvement by physical examination, standardized blood tests, electrocardiogram (ECG), echocardiogram (ECHO), chest X-ray, pulmonary function tests, and a 24-h urine collection.^{19–22} Cardiac involvement was indicated by septal or left ventricular posterior wall thickening >12 mm on ECHO in the absence of a history of hypertension or valvular heart disease, or in the presence of unexplained low voltage (<0.5 mV) on ECG, and/or by a clinical syndrome of CHF as per New York Heart Association (NYHA) classification. Patients with NYHA class 2 or higher CHF with evidence of cardiac involvement by ECHO and/or ECG were stratified as having predominant cardiac involvement. Renal involvement was indicated by proteinuria of

>500 mg/24 h or an elevated serum creatinine >2.0 mg/dl, in the absence of other causes of renal disease. Gastrointestinal involvement was indicated by involuntary loss of 10% of the normal body weight or diarrhea unexplained by other gastrointestinal disorders. Liver involvement was indicated by hepatomegaly >4 cm below the right costal margin on physical examination, or alkaline phosphatase >2 × normal value. Neurologic syndromes included symptoms or signs of peripheral sensory or motor neuropathy, or autonomic neuropathy associated with orthostatic hypotension (ie a drop in blood pressure of >20 mm upon standing when in euolemic state). Performance status was assessed according to the Southwest Oncology Group (SWOG) criteria by at least two clinicians independently. All patients were evaluated by a hematologist and cardiologist and, when appropriate, by nephrology, pulmonary, gastroenterology, or neurology specialists.

Eligibility criteria

The eligibility criteria for this trial included a tissue diagnosis of amyloidosis, with evidence of an underlying plasma cell dyscrasia, within 1 year of enrollment and no prior chemotherapy. Other eligibility criteria included age >18 years, amyloid disease involvement of at least one major organ system (cardiac, renal, GI/liver, neuropathy), minimum measures of performance status (SWOG <3), cardiac function (LVEF >40%), pulmonary function (room air O₂ saturation >95%), and hemodynamic stability (supine systolic blood pressure of >90 mm Hg). Patients on dialysis for renal failure were not excluded, if other eligibility criteria were met. It was required that patients meet these eligibility criteria both at the time of enrollment and prior to the start of stem cell collection, in order to proceed to HDM/SCT treatment.

Study design and treatment plan

Enrolled patients were randomized to receive HDM/SCT as initial treatment, Arm-1, or to receive two cycles of oral melphalan and prednisone followed by HDM/SCT, Arm-2. In each arm, the patients were stratified according to predominant organ involvement of cardiac, renal, or others (included gastrointestinal, liver or neuropathy), and within the time periods of 0–3 or 4–12 months from diagnosis to referral. The assignment of the patient's stratum was made after clinical evaluation determining the predominant organ affected. Patients randomized to Arm-2 received two cycles of oral melphalan and prednisone in a standard dosing schedule, that is, melphalan 0.2 mg/kg/day for 4 days with prednisone 1.0 mg/kg/day for 4 days, the second cycle given 6 weeks after the first.¹⁰

Stem cells were collected following G-CSF mobilization and a minimum collection of 2.0×10^6 CD-34+ cells/kg was required to proceed with high-dose chemotherapy. The protocol permitted a supplemental bone marrow harvest, in addition to peripheral blood stem cell collection, to achieve a minimum yield of stem cells required for HDM/SCT. Depending on age and cardiac status, patients received either full high-dose melphalan at 200 mg/m² or modified high-dose melphalan at 140 mg/m² (age >61 years or LVEF

<45%) in a divided dose over 2 days. Stem cell infusions were performed 24 h after patients completed high-dose chemotherapy.

Measurements of treatment response

The primary outcome measure for this trial was survival assessed for all patients randomized. Patients who completed HDM/SCT were assessed for hematologic and clinical responses at 3 months, 12 months, and annually thereafter. A complete hematologic response (CR), determined at 1 year of follow-up, required that there be no evidence of a persistent plasma cell dyscrasia in the bone marrow, or persistent monoclonal gammopathy detectable by immunofixation electrophoresis of serum and urine proteins. Patients with evidence of a persistent clonal plasma cell disorder were termed noncomplete responders (non-CR). Clinical responses were defined for each organ system involved, irrespective of stratification, and measured at 1 year. Performance status was also reassessed at this time.

Statistical analysis

This randomized study was designed to have 80% power for detection of a 25% difference in the proportion of subjects surviving for at least 1 year between the two treatment arms. This power calculation assumed a two-sided test with a significance level of 0.05.

Fisher's exact test was used to compare the treatment groups with respect to clinical characteristics, including the numbers of patients with one or more organ systems involved, and numbers completing treatment. The *t*-test was used to compare the treatment groups with respect to age and interval from diagnosis to study enrollment. The survival of patients in each arm was depicted using Kaplan–Meier survival plots, and equality between survival curves was tested by the likelihood ratio test. Among those who completed treatment, Fisher's exact test was used to compare the treatment groups with respect to numbers of patients who received the higher dose of melphalan and to compare those who did or did not achieve the secondary outcome of hematologic response at 1 year, with respect to whether or not any organ systems improved. In all analyses, *P*-values reflect two-sided test results.

Results

Patient characteristics

In all, 52 patients were randomized to Arm-1 and 48 to Arm-2 (Table 1). The median age and gender of patients were similar within each arm. The majority of patients in both arms had more than one organ system involved, 73% in Arm-1 and 75% in Arm-2, and the frequency of system involvement was similar in both. Single organ involvement was most often renal and occurred in 13% (7/52) of patients in Arm-1 and in 19% (9/48) of patients in Arm-2. Three patients in each arm were on hemodialysis for end-stage renal failure from amyloid-related kidney involve-

Table 1 Patient characteristics

	Arm-1	Arm-2
Patients enrolled	52	48
Median age (years)	57	55
M:F	34:18	30:18
<i>Organ involvement n (%)</i>		
Renal	44 (85%)	39 (82%)
Renal only	9	11
Hemodialysis	3	3
Cardiac	24 (46%)	22 (46%)
CHF compensated	9	11
GI/Liver	28 (54%)	24 (50%)
Neuropathy	22 (42%)	21 (44%)
Soft tissue	12 (23%)	9 (19%)
<i>Light-chain isotype n (%)</i>		
Kappa	5 (10%)	4 (8%)
Lambda	47 (90%)	44 (92%)

Table 2 Patient stratification and treatment

	Arm-1	Arm-2
<i>Stratification by dominant organ n (%)</i>		
Cardiac	11 (21%)	11 (23%)
Renal	29 (56%)	27 (56%)
Other	12 (23%)	10 (21%)
<i>Stratification by time from diagnosis n (%)</i>		
0–3 months	33 (63%)	35 (73%)
> 3–12 months	19 (37%)	13 (27%)
Median time from enrollment to HDM/SCT ^a	6 weeks	15 weeks
Patients completing HDM/SCT n (%)	43 (83%)	32 (67%)
<i>IV melphalan dose</i>		
200 mg/m ²	32 (74%)	26 (81%)
140 mg/m ²	11 (26%)	6 (19%)
<i>Treatment-related mortality</i>		
Prestem cell collection	0 (0%)	6 (13%)
Stem cell mobilization and collection	5 (10%)	7 (15%)
Death within 90 days of HDM/SCT	5 (10%)	4 (8%)

^aHigh-dose melphalan and stem cell transplantation.

ment. The types of monoclonal gammopathy, ie κ vs λ , were similar in the two arms: 90% (47/52) of patients had λ light chains in Arm-1 and 92% (44/48) of patients had λ light chains in Arm-2.

The number of patients within each stratum and the time periods from diagnosis showed that the two arms were well balanced (Table 2). The median interval from diagnosis to enrollment was 81 days (11.5 weeks) for Arm-1 and 65 days (9 weeks) for Arm-2 ($P=0.231$). The median time from enrollment to HDM/SCT differed, however, on account of the study design (6 weeks for Arm-1 vs 15 weeks for Arm-2).

HDM/SCT treatment

In all, 83% (43/52) of patients in Arm-1 completed HDM/SCT, while only 67% (32/48) of patients completed HDM/SCT in Arm-2 ($P=0.06$) (Table 2). Of the nine patients who did not complete treatment in Arm-1, four patients withdrew from the study and five patients had death or

complications during stem cell mobilization and collection. Two of the five patients died suddenly 3 and 9 days after beginning stem cell mobilization, and three others became too ill to proceed with treatment. Three of the five patients had been assigned to the cardiac stratum, but all had cardiac organ involvement at evaluation.

In total, 16 patients did not complete treatment in Arm-2. Of these, one patient withdrew from the study, two were withdrawn after unrelated disease (adenocarcinoma of the colon, myelodysplastic syndrome) developed disqualifying them for treatment, three patients died during the initial oral chemotherapy phase of treatment, and three had disease progression making them ineligible for treatment. Seven additional patients began stem cell mobilization, but did not receive HDM/SCT. Of these, two died suddenly 1 and 3 days after beginning stem cell mobilization, one died of a thromboembolism 10 days after beginning stem cell mobilization, and four patients were too ill to proceed with HDM. Of the 16 patients who did not complete treatment in Arm-2, 14 had cardiac organ involvement at evaluation, of whom six had been assigned to the cardiac stratum. Disease progression was the major reason for the difference in number of patients completing HDM/SCT in Arm-1 and Arm-2, although the additional time required to have oral chemotherapy before HDM/SCT for the patients in Arm-2 was on average only 9 weeks. Of the patients who received HDM/SCT, the proportion who received full high-dose melphalan (200 mg/m²) in Arm-1 and Arm-2 and those who received modified high-dose melphalan (140 mg/m²) were similar ($P=0.58$).

Stem cell mobilization and collection

Initial treatment with two cycles of oral chemotherapy did not interfere with subsequent stem cell collection. The median number of large volume leukaphereses required to achieve the minimal yield of stem cells was two in both arms (range 1–5). Similarly, the median number of stem cells collected in both arms were similar: 5.8×10^6 CD-34+ /kg (range $1.2\text{--}17.1 \times 10^6$ CD-34+ /kg) in Arm-1 and 4.8×10^6 CD-34+ /kg (range $0.9\text{--}11.5 \times 10^6$ CD-34+ /kg) in Arm-2. Three patients required a supplemental bone marrow harvest in order to achieve the minimal CD-34+ cell dose required to proceed to high-dose chemotherapy because of an inadequate peripheral blood stem cell collection (two patients in Arm-1 and one in Arm-2).

Treatment-related mortality and toxicities

Treatment-related mortality, defined as any death occurring after enrollment on the study up to 90 days after HDM/SCT, occurred in 27 patients (27%), 10 in Arm-1 and 17 in Arm-2 ($P=0.076$). In Arm-1, no patients died before stem cell mobilization, five died during stem cell mobilization or following initiation of stem cell mobilization due to disease progression that did not allow them to proceed to HDM/SCT, and five died within 90 days of completing HDM/SCT. In Arm-2, six patients died of disease progression that did not allow them to initiate stem cell mobilization, seven patients died during stem cell mobilization or of disease progression that did not allow

Table 3 Frequency of National Cancer Institute Grade >2 toxicities

Toxicities	Arm 1 (n = 43)	Arm 2 (n = 32)
Nausea or vomiting	24 (56%)	15 (47%)
Diarrhea	14 (33%)	8 (25%)
Mucositis	22 (51%)	15 (47%)
Pulmonary edema	10 (23%)	2 (6%)
Gastrointestinal bleeding	5 (12%)	2 (6%)
Nongastrointestinal bleeding	5 (12%)	1 (3%)
Hepatic	25 (58%)	20 (62%)
Renal	9 (21%)	8 (25%)
Febrile neutropenia	29 (67%)	17 (54%)
Sepsis	3 (7%)	0 (0%)

them to proceed to HDM/SCT, and four died within 90 days of completing HDM/SCT.

Treatment-related toxicities were similar in the two treatment arms for patients who completed HDM/SCT (Table 3). It is noteworthy that two patients in Arm-1 developed spontaneous rupture of the spleen in the peritransplant period (D+16 and D+23, respectively), and were successfully treated with emergency splenectomy. One of these patients had evidence of a coagulopathy from factor X deficiency at the time of treatment.

Survival

The median survival of patients in both treatment arms did not differ significantly, although the survival curves suggest a trend for early survival advantage in Arm-1 (Figure 1). The overall survival of patients at 1 and 2 years after randomization appeared slightly higher for patients in Arm-1 (67% and 60%) than for those in Arm-2 (56 and 54%). However, with a median follow-up of 45 months for all patients enrolled on this study (range 24–70 months), median survival was not reached for Arm-1, but was 37 months for Arm-2, a nonsignificant difference ($P=0.39$). The overall survivals at 48 and 60 months were 51 and 51% for Arm-1, compared to 50 and 39% for Arm-2 from the time of randomization.

The survival of patients within each randomized disease stratum also did not differ between the treatment arms, and was worse for patients randomized to the cardiac stratum in each. The risk associated with any cardiac involvement is seen when all patients with cardiac involvement, whether or not it was the predominant feature of their disease, were compared to all other patients in each treatment arm (Figure 2). Survival for patients with cardiac involvement was 9.6 months in Arm-1 and was 4.8 months in Arm-2 ($P=0.10$). As noted above, five patients with cardiac involvement in Arm-1 and 14 patients with cardiac involvement in Arm-2 were unable to complete treatment with HDM/SCT because of death or complications associated with treatment. Nonetheless, there was no difference in survival for the 43 patients on Arm-1 and the 32 patients on Arm-2 who were able to receive treatment with HDM/SCT (Figure 3).

As reported by others, the number of organ systems involved in amyloid disease (>2 vs <2) was found to be a strong determinant of survival. The organ systems included in this analysis were cardiac, renal, gastrointestinal/liver,

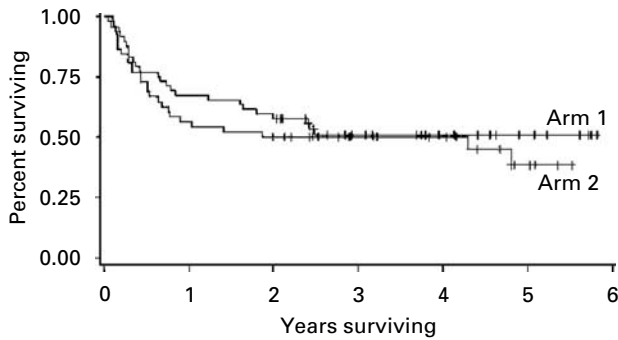


Figure 1 Overall survival from the time of randomization by treatment group – patients on Arm-1 ($n=52$) received HDM/SCT as initial therapy, while patients on Arm-2 ($n=48$) received two cycles of melphalan and prednisone prior to HDM/SCT. With a median follow-up of 45 months, median survival was not reached for Arm-1, but was 37 months for Arm-2 by Kaplan–Meier analysis ($P=0.39$).

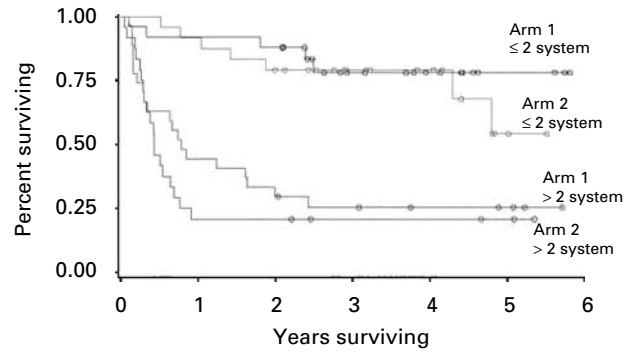


Figure 4 Overall survival from the time of randomization by treatment group and number of involved organ systems – the organ systems that were included in this analysis were cardiac, renal, gastrointestinal, neuropathy, and soft tissue. While median survival was not reached for patients with <2 organ systems involved in either treatment arm, median survival for patients with >2 organ systems involved was 9.3 months for patients in Arm-1 and 5.1 months for those in Arm-2 ($P=0.183$).

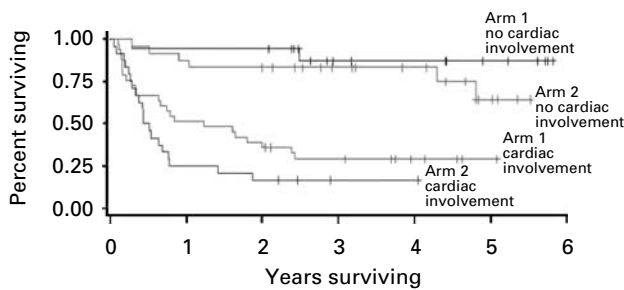


Figure 2 Overall survival from the time of randomization by treatment group, comparing patients with or without cardiac involvement. Median survival for patients with no ECG or ECHO evidence of cardiac disease has not been reached for both arms, and exceeds 72 months. For patients on Arm-1 with cardiac involvement ($n=24$) median survival was 9.6 months, while on Arm-2 ($n=22$) it was 4.8 months ($P=0.10$).

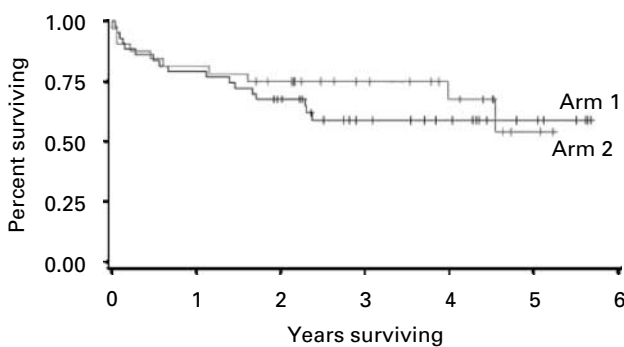


Figure 3 Overall survival by treatment group from time of HDM/SCT – there was no difference in survival for patients in the two treatment arms from the time of initiation of HDM/SCT.

nervous system, and soft tissues. While the median survival was not reached for patients with ≤ 2 organ systems involved in either treatment arm, median survival had been reached for patients with >2 organ systems involved in both arms (9.3 months; Arm-1, 5.1 months; Arm-2, $P=0.183$) (Figure 4).

Hematologic and clinical responses

Hematologic responses were evaluated for all surviving patients who completed HDM/SCT at 1 year following treatment. There were no differences in complete hematologic responses among patients evaluated a year after completion of HDM/SCT in Arm-1 and Arm-2: 32% (11/34) in Arm-1 vs 30% (8/26) in Arm-2 ($P=1.00$). Moreover, there was no difference in complete hematologic response among patients who were enrolled in Arm-1 and Arm-2: 21% (11/52) in Arm-1 vs 17% (8/48) in Arm-2, intention to treat analysis. All but one of the hematologic CRs were observed in patients who had received full high-dose melphalan (200 mg/m^2), and these patients represented the great majority of patients surviving for >1 year (67% of all patients enrolled in Arm-1, 56% of all patients enrolled in Arm-2).

Changes in organ function and performance status were measured at 1 year following treatment for all surviving patients (Table 4). Improvements were measured for all systems that have a potential to improve, including renal, cardiac, gastrointestinal, liver, and peripheral or autonomic neuropathy, and for performance status that was poorer than SWOG 1 on evaluation. In all, 42% of the patients, who were evaluated at 1 year after treatment, whether or not they had achieved a CR, had an improvement after treatment with HDM/SCT. Clinical responses were more evident among patients who achieved a hematologic CR (63%, 12/19), than among those who did not (35%, 13/39), regardless of treatment arm ($P=0.048$).^{31,32} This difference was most notable in the renal (6/16 vs 5/31) and cardiac (1/3 vs 1/12) groups.

Discussion

Our previous reports of treatment with HDM/SCT in AL amyloidosis suggest that it is superior to other therapy for AL amyloidosis. This trial was undertaken to determine whether or not a short initial course of treatment with oral melphalan and prednisone prior to aggressive treatment

Table 4 Clinical response^a

Organ	Arm-1 CR	Arm-1 non-CR	Arm-2 CR	Arm-2 non-CR
Renal ^b	4/9	3/18	2/7	2/13
GI/Liver ^c	0/5	4/9	5/7	1/3
Cardiac ^d	1/2	0/9	0/1	1/3
Neuropathy ^e	2/4	6/10	2/4	1/2
PS ^f	6/11	5/20	3/8	0/16
>1 of above	6/11	10/23	6/8	3/16

^aNumber improved/number involved at baseline of patients surviving and evaluated at 1 year, separated by hematologic CR (complete response) or non-CR (partial response + no response).

^bResponse defined as >50% reduction on proteinuria with <25% decrease in creatinine clearance.

^cResponse defined as improvement in symptoms of diarrhea and weight loss, and/or decrease in hepatomegaly decrease of >2 cm, and/or >50% reduction in alkaline phosphatase, depending on baseline abnormality.

^dResponse defined as decrease in interventricular septum of >2 mm by ECHO and/or clinical improvement in CHF (decrease in diuretic requirement).

^eResponse defined as normalization of symptoms associated with peripheral and/or autonomic neuropathy.

^fPS = SWOG performance status; response defined as improvement of >1 unit.

with HDM/SCT improves survival and hematologic response for newly diagnosed patients with AL amyloidosis. The patients in this study include those with cardiac or multisystem disease who have been reported to have poor survival.¹⁰ By design, we included only newly diagnosed and untreated patients, and thus we did not exclude those likely to have early deaths and did not include those who have benefited from prior therapies. Results of this study indicate that previously untreated patients with AL amyloidosis had no additional benefit from initial treatment with oral chemotherapy prior to HDM/SCT with respect to survival, hematologic response, or the likelihood of eventual clinical improvement. Instead, we found that some patients with AL amyloidosis, particularly those with cardiac involvement, appeared to suffer a survival disadvantage if HDM/SCT was delayed by initial treatment with standard oral chemotherapy.

The delay in HDM/SCT caused by initial treatment with oral melphalan and prednisone (Arm-2) was only about 9 weeks on average. Nonetheless, six of the 48 patients randomized to this treatment arm (6/48 or 13%) did not proceed to HDM/SCT because of clinical deterioration that led to death. This result emphasizes not only the relentlessly progressive nature of AL amyloidosis, but also the relative ineffectiveness of standard oral chemotherapy in arresting disease progression, particularly when cardiac involvement is present. On the other hand, the short course of oral chemotherapy did not appear to interfere with stem cell collection or increase toxicity; thus, patients who have received modest doses of oral melphalan can still be treated with high-dose chemotherapy if they meet the eligibility criteria.

One of the objectives of this study was to determine if an initial course of oral chemotherapy prior to HDM/SCT might increase the likelihood of complete hematologic responses. However, there was no difference in hematologic responses between the two treatment arms for patients who completed HDM/SCT. It should be noted that in this study

the complete hematologic response rates were somewhat lower than those that we have reported previously.^{19,20,21} The reasons for these differences likely include the less restrictive eligibility criteria used in this trial, together with the use of more sensitive immunofixation electrophoresis techniques in determining complete hematologic responses. In the past, it has been difficult to quantify partial hematologic responses in AL amyloidosis, since there have been no accurate quantitative measures of amyloid protein production. However, a new quantitative free light-chain assay may provide a mean for stratifying partial hematologic responses in future trials.³³ Nonetheless, treatment benefits were evident in this trial, as the organ system improvements occurred in many patients who did not achieve a hematologic CR. In our experience, relapses are uncommon among individuals who have achieved a complete hematologic response at 1 year following HDM/SCT, and relapses have not been observed among patients treated in this trial with a median follow up of 45 months.

Untreated AL amyloidosis is in almost all cases a progressive and fatal disease, and long-term survival has only rarely been observed with oral melphalan and prednisone treatment. Development of peripheral blood stem cell transplantation with growth factor support has allowed for more aggressive treatment of these patients, and it has been shown that this treatment can result in durable complete remissions and major improvements in organ function. While these observed outcomes are promising, HDM/SCT remains a high-risk form of treatment in AL amyloidosis,³⁴ and future studies of HDM/SCT should focus on improving supportive care to limit treatment-related morbidity and mortality, and on developing strategies to improve hematologic CR rates and survival. Such strategies might include the use of thalidomide, since thalidomide has been shown to have some activity in AL amyloidosis.³⁵ It is possible that a regimen of thalidomide alone or in combination with dexamethasone given before or following HDM/SCT might increase hematologic responses and survival in patients with AL amyloidosis.³⁵⁻³⁷ However, based on our's and others' experience with the toxicity of this regimen in patients with AL amyloidosis, this should not be tried outside the auspices of a clinical trial.

In conclusion, our results highlight the importance of early diagnosis and timely institution of aggressive antiplasma cell therapy for patients with AL amyloidosis, a progressive and fatal disorder, particularly for patients with evidence of cardiac involvement at the time of diagnosis.

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