

ORIGINAL ARTICLE

High-Dose Melphalan versus Melphalan plus Dexamethasone for AL Amyloidosis

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ABSTRACT

BACKGROUND

High-dose chemotherapy followed by autologous hematopoietic stem-cell transplantation has been reported to provide higher response rates and better overall survival than standard chemotherapy in immunoglobulin-light-chain (AL) amyloidosis, but these two strategies have not been compared in a randomized study.

METHODS

We conducted a randomized trial comparing high-dose intravenous melphalan followed by autologous hematopoietic stem-cell rescue with standard-dose melphalan plus high-dose dexamethasone in patients with AL amyloidosis. Patients (age range, 18 to 70 years) with newly diagnosed AL amyloidosis were randomly assigned to receive intravenous high-dose melphalan plus autologous stem cells or oral melphalan plus oral high-dose dexamethasone.

RESULTS

Fifty patients were enrolled in each group. The results were analyzed on an intention-to-treat basis, with overall survival as the primary end point. After a median follow-up of 3 years, the estimated median overall survival was 22.2 months in the group assigned to receive high-dose melphalan and 56.9 months in the group assigned to receive melphalan plus high-dose dexamethasone ($P=0.04$). Among patients with high-risk disease, overall survival was similar in the two groups. Among patients with low-risk disease, there was a nonsignificant difference between the two groups in overall survival at 3 years (58% in the group assigned to receive high-dose melphalan vs. 80% in the group assigned to receive melphalan plus high-dose dexamethasone; $P=0.13$).

CONCLUSIONS

The outcome of treatment of AL amyloidosis with high-dose melphalan plus autologous stem-cell rescue was not superior to the outcome with standard-dose melphalan plus dexamethasone. (ClinicalTrials.gov number, NCT00344526.)

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N Engl J Med 2007;357:1083-93.
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THE ORIGIN OF AMYLOID IN SYSTEMIC immunoglobulin-light-chain (AL) amyloidosis is a clone of plasma cells in the bone marrow that synthesizes monoclonal immunoglobulin light chains. In tissues, these light chains aggregate into amyloid fibrils. The accumulation of amyloid deposits in vital organs leads to progressive disability and death. Life expectancy depends on the degree of organ involvement and ranges from a few years to less than 6 months for patients with severe cardiomyopathy.¹ In the mid-1990s, two randomized trials showed that standard-dose chemotherapy with melphalan and prednisone could prolong survival in patients with AL amyloidosis,^{1,2} but clinical responses were rare and overall survival was extended by only a few months.

High-dose melphalan with autologous hematopoietic stem-cell rescue was introduced in the early 1990s, and it is increasingly used to treat patients with AL amyloidosis. However, transplant-related mortality is high, ranging between 13% (in referral centers) and 43% (in a French retrospective multicenter study).³⁻⁵ The survival benefit of high-dose melphalan has been attributed to a patient-selection bias,⁶ but a case-control study suggested a survival advantage for high-dose melphalan plus hematopoietic stem-cell rescue as compared with conventional treatment.⁷ The present study is a randomized comparison of high-dose melphalan plus autologous hematopoietic stem-cell rescue with standard-dose melphalan plus high-dose dexamethasone in patients with AL amyloidosis.

METHODS

PATIENTS

Patients between 18 and 70 years of age who had biopsy-proven systemic AL amyloidosis, who had received no more than two previous courses of any chemotherapy regimen, who did not have symptomatic multiple myeloma, and who had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 2 or lower were eligible. The inclusion criteria were a histologic diagnosis of amyloidosis and either immunohistochemical characterization of the amyloid deposits or evidence of a monoclonal immunoglobulin protein in the serum or urine specimen or a monoclonal staining pattern of bone marrow plasma cells.

When immunohistochemical characterization was lacking, an effort was made to rule out hereditary amyloidosis by taking into account the patient's family history and the pattern of organ involvement.

The protocol was approved by the local ethics committee, and all of the patients gave their written informed consent. Randomization was based on a balanced randomization list with the use of blocks of variable size, stratified according to age (younger than 65 years or 65 years or older) and according to the affected organ system (cardiac, renal, neurologic, or other).

TREATMENT

Patients in the group assigned to receive melphalan plus dexamethasone received monthly courses of oral melphalan (10 mg per square meter of body-surface area on days 1 to 4) plus high-dose oral dexamethasone (40 mg per day on days 1 to 4) for up to 18 treatment courses if no severe adverse effects occurred. In January 2002, when 43 patients had been included, the protocol was amended to permit discontinuation of treatment after 12 courses if a complete hematologic remission occurred. The dose of melphalan was adjusted during the first three courses in order to induce mild cytopenia (white-cell count, <3000 per cubic millimeter) at midcourse. Prophylaxis with proton-pump inhibitors and trimethoprim-sulfamethoxazole (one double-strength tablet thrice weekly) was recommended.

In the group assigned to receive high-dose melphalan, autologous hematopoietic stem cells were obtained from the peripheral blood with granulocyte colony-stimulating factor (G-CSF) (5 μ g per kilogram of body weight subcutaneously, twice daily). Cytapheresis was performed on day 5, with the use of the procedure described in the Supplementary Appendix, available with the full text of this article at www.nejm.org. The goal was to collect 2×10^6 CD34+ cells per kilogram. If this goal was not achieved, a second attempt to obtain the cells was permitted. Patients then received melphalan, 200 mg per square meter given intravenously on day 0, and stem cells were infused on day 2. The dose of melphalan was reduced to 140 mg per square meter for patients 65 years of age or older and for those with an ejection fraction below 30%, a calculated creatinine clearance of less than 30 ml per minute, or severe liver dis-

ease (prothrombin index, <50%; total bilirubin or alkaline phosphatase level, >5 times the normal level). G-CSF was administered subcutaneously daily from day 7 until neutropenia resolved. Transfusions to maintain the platelet count at more than 50,000 per cubic millimeter were recommended.

ASSESSMENT OF ORGAN INVOLVEMENT, RESPONSES, AND OUTCOME

Organ involvement and the response to therapy were evaluated according to the international consensus guidelines,⁸ except that bone marrow studies were not required to define a complete response (Table 1). Hematologic and clinical responses were analyzed only in patients who received three or more courses of melphalan plus dexamethasone and in patients who survived for more than 3 months after stem-cell transplantation. A clinical response was defined as improvement of an

organ known to be involved with amyloid. A complete hematologic response was defined as the complete disappearance of the monoclonal immunoglobulin or light chain in a serum or urine specimen; a partial hematologic response was defined as more than a 50% reduction in these proteins. Light-chain levels in serum were assessed, whenever possible, with the free light-chain assay (Free-lite, Binding Site),⁹ which became available for use in this trial in 2003.

STATISTICAL ANALYSIS

The number of patients required for the study was calculated with the use of the log-rank test. The working hypothesis was that high-dose melphalan would improve the survival rate (estimated to be 55.5% in the group assigned to receive melphalan plus dexamethasone) by 25% at 18 months, with a type 1 error rate of 5% and a statistical pow-

Table 1. Criteria for Organ Involvement, Organ Response, and Hematologic (Immunochemical) Response.*

Organ involvement

Kidney: 24-hr urinary protein >0.5 g/day, predominantly albumin

Heart: Mean wall thickness >12 mm on echocardiogram, no other cardiac disease responsible for the increase in wall thickness

Liver: Total liver span >15 cm in the absence of heart failure, or alkaline phosphatase level >1.5 times upper limit of normal

Nerve: Symmetric sensorimotor peripheral neuropathy in the legs, gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration

Gastrointestinal tract: Symptoms and verification by means of biopsy

Lung: Symptoms and verification by means of biopsy, interstitial radiographic pattern

Soft tissue: Tongue enlargement, arthropathy, skin purpura, myopathy (pseudohypertrophy or detected by means of biopsy), lymph node involvement, carpal tunnel syndrome

Organ response

Heart: Mean interventricular septal thickness decreased by 2 mm, 20% improvement in ejection fraction, improvement by two New York Heart Association classes without an increase in diuretic use, and no increase in wall thickness

Kidney: 50% decrease (a decrease of at least 0.5 g/day) in 24-hr urinary protein (must be >0.5 g/day before treatment), creatinine and creatinine clearance must not worsen by 25% over baseline level

Liver: 50% decrease in abnormal alkaline phosphatase value, at least 2-cm decrease in liver size on radiographic imaging

Nerve: Improvement in nerve conduction velocity on electromyogram (rare)

Hematologic (immunochemical) response

Complete response: Serum and urine negative for a monoclonal protein by means of immunofixation, normal kappa:lambda free light-chain ratio, and normal absolute value of the involved serum free light-chain (in patients without renal insufficiency)

Partial response: Serum M component >0.5 g/dl and 50% reduction; light chain in the urine with a visible peak >100 mg/day and 50% reduction; or free light chain >10 mg/dl and 50% reduction

Progression after complete response: Any detectable monoclonal protein or abnormal free light-chain ratio (light chain must double)

Progression after partial response or stable response: 50% increase in serum M protein to >0.5 g/dl or 50% increase in urinary M protein to >200 mg/day with a visible peak; free light-chain increase of 50% to >10 mg/dl

Stable: No complete response, partial response, or progression

* Data are adapted from Gertz et al.⁸

Table 2. Baseline Characteristics of the Patients.*

Characteristic	Group Assigned to Melphalan plus Dexamethasone	Group Assigned to High-Dose Melphalan	P Value
Time from diagnosis to randomization (days)			
Median	41	50	0.28
Range	9–287	8–1194	
Male sex (no.)	30	27	0.37
Age			
Mean (yr)	59.1±6.9	56.8±7.6	0.10
≥65 yr (no.)	10	8	0.27
High-risk disease (no.)	20	21	0.84
ECOG performance-status score (no.)			0.48
0	9	11	
1	25	19	
2	16	20	
NYHA category (no.)			0.87
1	9	8	
2	7	10	
3	4	3	
4	3	3	
Organs involved (no.)			0.98
1	16	17	
2	16	15	
3	13	12	
≥4	5	6	
Heart involvement (no.)	23	24	0.84
Left ventricular ejection fraction			
Mean (%)	61.3±15.4	54.9±13.9	0.21
30–50% (no.)	4	6	0.88
Interventricular septum			
Mean (mm)	17.4±2.9	16.8±2.9	0.48
>15 mm (no.)	15	15	0.63
Kidney involvement (no.)	34	35	0.83
Serum creatinine (mg/dl)			
Mean	121.4±111.7	118.0±65.1	0.88
24-hr urinary protein			
Mean (g/24 hr)	6.7±5.1	7.71±5.3	0.43
>3 g/24 hr (no.)	26	28	0.55
Serum albumin (g/dl)	24.0±8.9	22.2±10.8	0.45
Liver involvement (no.)	10	16	0.17
Serum alkaline phosphatase			
Mean (IU/liter)	735.3±669.3	489.6±637.0	0.36
>2× ULN (no.)	5	8	0.99

Table 2. (Continued.)

Characteristic	Group Assigned to Melphalan plus Dexamethasone	Group Assigned to High-Dose Melphalan	P Value
Nerve involvement (no.)	10	12	0.63
Serum monoclonal immunoglobulin (g/dl)	10.4±7.1	10.4±7.9	0.99
Monoclonal FLC (mg/liter)			
Median	250	173.0	0.49
Range	9–1290	13.9–5460.0	
Bone marrow plasma cells			
Median (%)	7.5	6.5	0.19
Range (%)	0.0–79.0	1.0–30.0	
>30% (no.)	2	0	0.54

* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group, NYHA New York Heart Association, ULN upper limit of the normal range, and FLC free light chain.

er of 80%.¹⁰ Thus, a minimum of 46 patients per group was required, with a total in both groups of at least 25 deaths. We decided to include a total of 100 patients.

The data were analyzed on an intention-to-treat basis. Descriptive analyses were based on frequencies for qualitative variables and means, standard deviations, and medians for quantitative variables. Comparisons were made with the use of the Student's t-test or the Mann–Whitney U test. Frequencies were compared with the use of the chi-square test or Fisher's exact test.

Survival analyses according to the treatment group and organ involvement were based on the Kaplan–Meier method with the use of the log-rank test and a univariate Cox proportional-hazards regression analysis. A two-sided P value of less than 0.05 was considered to indicate statistical significance. The start date was the date of randomization, and the cutoff date was August 15, 2006.

Subgroup analyses of patients with low-risk and those with high-risk AL amyloidosis were planned on the basis of the Mayo Clinic criteria. Patients with low-risk disease have all the following: an interventricular cardiac septum thickness of less than 15 mm, an ejection fraction of more than 55%, a serum creatinine level of 2 mg per deciliter (177 μ mol per liter) or less, and a direct bilirubin value of 2 mg per deciliter (34 μ mol per liter) or less.⁶

A landmark analysis was also performed to study the efficacy of the two strategies indepen-

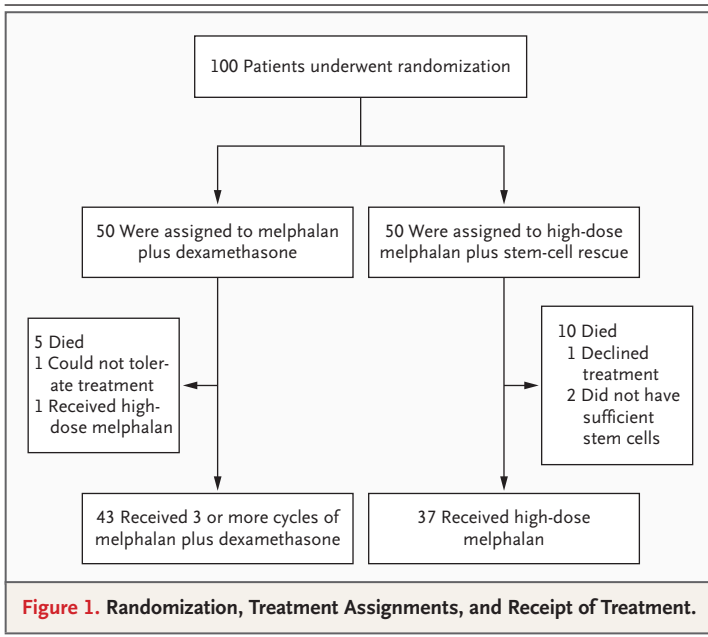
dently of early toxic effects. This analysis focused on patients who survived for at least 6 months after randomization and who received their assigned treatment (either high-dose melphalan or three or more courses of melphalan plus high-dose dexamethasone).¹¹

RESULTS

Between January 11, 2000, and January 7, 2005, 100 patients were enrolled in 29 centers (Fig. 1). Two patients who had previously received three cycles of standard-dose chemotherapy were not excluded from the group assigned to receive melphalan plus dexamethasone, since this was considered a minor deviation from the inclusion criteria.

Table 2 shows the baseline characteristics of the 100 patients. The AL amyloidosis type was determined by means of immunohistochemical analysis in 60 patients. All of the other patients had a monoclonal protein in blood or urine specimens and clinical features that were characteristic of AL amyloidosis. The AL type of amyloid was confirmed by means of immunohistochemical analysis in all five patients who had normal serum levels of kappa and lambda free light chains at diagnosis.

The characteristics of amyloid disease were well balanced between the two groups of patients (Table 2). A total of 47 patients had cardiac involvement, 69 patients had renal involvement, 22 patients had nerve involvement, and 26 patients had



liver involvement. The median number of organs involved was two (range, one to five). Sixteen patients in the group assigned to melphalan plus dexamethasone and 17 patients in the group assigned to high-dose melphalan had only one affected organ.

TREATMENT

Of the 50 patients in the group assigned to high-dose melphalan, 13 did not receive the planned treatment (Fig. 1). Of the patients who did not receive the planned treatment, 1 patient declined treatment, 2 patients had an insufficient stem-cell harvest, and 10 patients died (8 patients died suddenly or had progressive heart failure, 1 had progressive hepatic amyloidosis, and 1 had sepsis). One patient's condition worsened before treatment with G-CSF began, and the patient died 40 days after undergoing randomization. Four patients died during treatment with G-CSF. No deaths occurred during leukapheresis. Five patients died between 11 and 45 days after stem-cell collection.

The median number of stem-cell harvests was two (range, 1 to 3); sufficient numbers of stem cells were collected after one course of G-CSF in 35 patients and after two courses of G-CSF in 2 patients. The median number of harvested CD34+ cells was 4.48×10^6 per kilogram (range, 0.68 to 11.0).

Of the 37 patients who received stem cells, 10 were given melphalan at a dose of 140 mg per

square meter and 27 were given melphalan at a dose of 200 mg per square meter. Of these 37 patients, 9 died within 100 days after receiving high-dose melphalan — 5 from multiorgan failure with acute renal failure, 2 from sepsis, and 2 from cardiac arrhythmia. The transplant-related mortality was 24%. In total, 19 patients died within 130 days after randomization. In 11 patients, the serum creatinine level increased to more than three times the baseline level, and 8 patients required hemodialysis.

In the group assigned to melphalan plus dexamethasone, two patients died early of cardiac arrhythmia — one before receiving any treatment and one on the third day of the first course of treatment. Five other patients died within 130 days after randomization, all from disease progression. Seven patients had toxic effects of grade 3 or more, 16 patients had grade 1 or 2 toxic effects, 10 patients had sepsis, 18 patients had cytopenia, and 1 patient had diabetes mellitus.

The median number of courses of melphalan plus dexamethasone received was 12 (range, 0 to 25). The median time between randomization and initiation of treatment with melphalan plus dexamethasone was 2 days (range, 0 to 41), and the median time between randomization and initiation of treatment with G-CSF was 8 days (range, 0 to 43). The median time between randomization and administration of high-dose melphalan was 36 days (range, 16 to 83).

HEMATOLOGIC RESPONSES

Forty-three patients in the group assigned to receive melphalan plus dexamethasone received three or more courses of treatment, and 29 patients in the group assigned to receive high-dose melphalan survived for more than 3 months after grafting.

In 65 of these patients (38 in the group assigned to receive melphalan plus dexamethasone and 27 in the group assigned to receive high-dose melphalan), hematologic responses could be evaluated by means of serum and urine electrophoresis, immunofixation, or both methods. The free light-chain assay could also be used to evaluate these responses.

Hematologic responses did not differ significantly between the two treatment groups (Table 3). They occurred in 26 patients in the group assigned to receive melphalan plus dexamethasone (68%) and in 18 patients in the group assigned to receive high-dose melphalan (66%); the response rates in

Table 3. Hematologic Response to Chemotherapy by Serum Free Light-Chain Assay, Conventional Techniques, and Both Approaches.

Response	Serum Free Light-Chain Assay		Conventional Techniques		Combined Approaches	
	Group Assigned to Melphalan plus Dexamethasone (N=19)	Group Assigned to High-Dose Melphalan (N=18)	Group Assigned to Melphalan plus Dexamethasone (N=35)	Group Assigned to High-Dose Melphalan (N=24)	Group Assigned to Melphalan plus Dexamethasone (N=38)	Group Assigned to High-Dose Melphalan (N=27)
Complete response — no.	9	11	12	9	12	11
Partial response — no.	5	2	12	6	14	7
Total — no. (%)	14 (74)	13 (72)	24 (69)	15 (62)	26 (68)	18 (67)
Intention-to-treat analysis — no./total no. (%)					26/50 (52)	18/50 (36)

the intention-to-treat analysis were 52% and 36%, respectively ($P=0.11$). Responses were evaluated by means of the free light-chain assay in 37 patients (19 in the group assigned to receive melphalan plus dexamethasone and 18 in the group assigned to receive high-dose melphalan). A complete remission was achieved in 9 patients (47%) in the group assigned to receive melphalan plus dexamethasone and in 11 patients (61%) in the group assigned to receive high-dose melphalan; 5 patients (26%) and 2 patients (11%), respectively, had partial remission, and no response was seen in 5 patients in each group.

The median levels of free light chains in serum at the time of best response after treatment were 28 mg per liter (range, 8 to 344) in the group assigned to receive melphalan plus dexamethasone and 26 mg per liter (range, 0.6 to 1140.0) in the group assigned to receive high-dose melphalan. Median pretreatment serum levels of true light chains in patients who underwent evaluation were 239 mg per liter (range, 32 to 1260) in the group assigned to receive melphalan plus dexamethasone and 118 mg per liter (range, 27 to 5460) in the group assigned to receive high-dose melphalan; normal serum values for kappa light chains range from 3.3 to 19.4 mg per deciliter, and normal serum values for lambda light chains range from 5.7 to 26.3 mg per deciliter.

ORGAN RESPONSES

Organ responses (Table 1) could be assessed in 73 patients. At least one response occurred in 39% of the patients (17 of 44) assigned to receive melphalan plus dexamethasone and in 45% of the patients (13 of 29) assigned to receive high-dose melphalan ($P=0.60$). In these two groups, renal responses occurred in 11 and 8 patients, hepatic responses occurred in 3 and 5 patients, cardiac

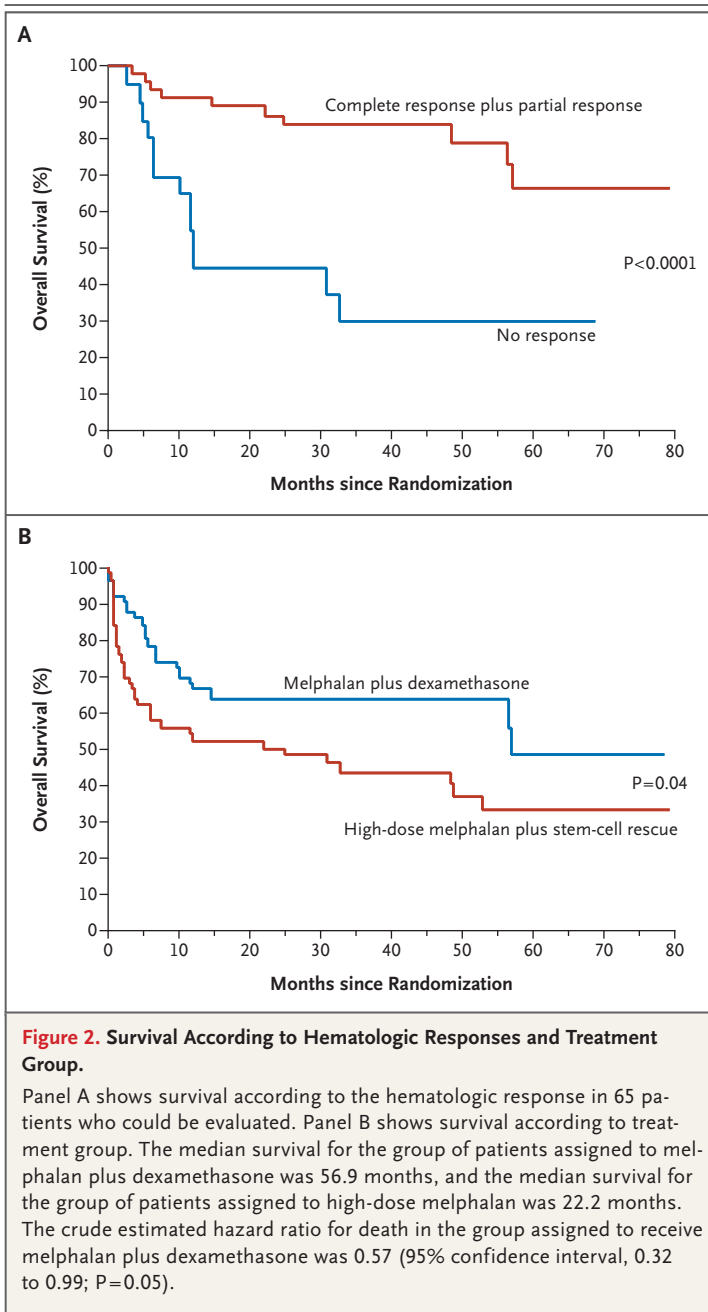
responses occurred in 3 and 4 patients, and neurologic responses occurred in 2 patients and 1 patient, respectively.

RELAPSES AND SALVAGE TREATMENT

Hematologic progression after the conclusion of treatment (Table 1) occurred in six patients in each group. The median time from randomization to hematologic progression was 32.5 months (range, 26 to 47) in the group assigned to receive melphalan plus dexamethasone and 32.0 months (range, 15 to 55) in the group assigned to receive high-dose melphalan. Three patients in the former group received second-line treatment with high-dose melphalan for resistant disease, with less than a partial response. Only one of these patients had a hematologic (complete) response. Other patients with disease progression or resistant disease received various other treatments, but none received more than one high-dose regimen.

OVERALL SURVIVAL

At the cutoff date of August 15, 2006, the median follow-up time for the entire cohort was 24 months, and for surviving patients it was 36 months. The median survival for the entire cohort was 48 months. Fifty-one patients died (20 in the group assigned to receive melphalan plus dexamethasone and 31 in the group assigned to receive high-dose melphalan) ($P=0.04$). At the cutoff date, among the surviving patients in the two groups, 23 of 30 patients assigned to receive melphalan plus dexamethasone and 11 of 19 patients assigned to receive high-dose melphalan did not receive additional chemotherapy; the performance-status score was 2 or more in 3 and 5 patients, respectively, and 3 patients and 1 patient, respectively, required long-term dialysis. Only the two late deaths (due to lung cancer and gastric cancer) in the group assigned



to receive melphalan plus dexamethasone were not directly related to amyloidosis or to the treatments received. Overall survival after randomization was strongly related to the rate of hematologic responses (Fig. 2A).

In the intention-to-treat analysis, the Kaplan–Meier estimate of median overall survival was 56.9 months in the group assigned to receive melphalan plus dexamethasone and 22.2 months in the group assigned to receive high-dose melphalan

($P=0.04$ by the log-rank test) (Fig. 2B). The crude estimated hazard ratio for death in the group assigned to receive melphalan plus dexamethasone was 0.57 (95% confidence interval [CI], 0.32 to 0.99; $P=0.05$). The hazard ratio did not change after adjustment for the main prognostic factors (performance status, number of organs involved, risk group, presence or absence of renal insufficiency, and presence or absence of cardiac involvement). Exclusion of the two patients who had received three courses of melphalan plus dexamethasone before enrollment did not affect these results.

On the basis of the Mayo Clinic criteria,⁶ 59 patients were at low risk for an adverse outcome of intensive treatment, and 41 were at high risk, mainly because of severe cardiac disease.⁶ The estimated 3-year overall survival rates were 70% among patients with low-risk disease and 25% among patients with high-risk disease ($P<0.001$) (Fig. 3A). Overall survival was similar in the two groups with high-risk disease ($P=0.27$). In the group with low-risk disease, overall survival at 3 years was 80% in the group assigned to receive melphalan plus dexamethasone and 58% in the group assigned to receive high-dose melphalan ($P=0.13$) (Fig. 3B). Among the 69 patients with renal involvement (proteinuria, defined as >0.5 g of protein per liter), the estimated 3-year overall survival rates were 70% in the group assigned to receive melphalan plus dexamethasone and 37% in the group assigned to receive high-dose melphalan ($P=0.02$).

In a landmark analysis of patients who survived for at least 6 months after randomization and who received their assigned treatment, there were 10 deaths among the 28 patients in the group assigned to receive high-dose melphalan and 8 deaths among the 37 patients in the group assigned to receive melphalan plus dexamethasone ($P=0.38$) (Fig. 3C).

DISCUSSION

This study, which was powered to show a 25% survival advantage with high-dose melphalan as compared with melphalan plus dexamethasone, did not show any superiority of high-dose melphalan over melphalan plus dexamethasone. On the contrary, the median overall survival was significantly longer (56.9 months) in the group assigned to receive melphalan plus dexamethasone than in the group assigned to receive high-dose

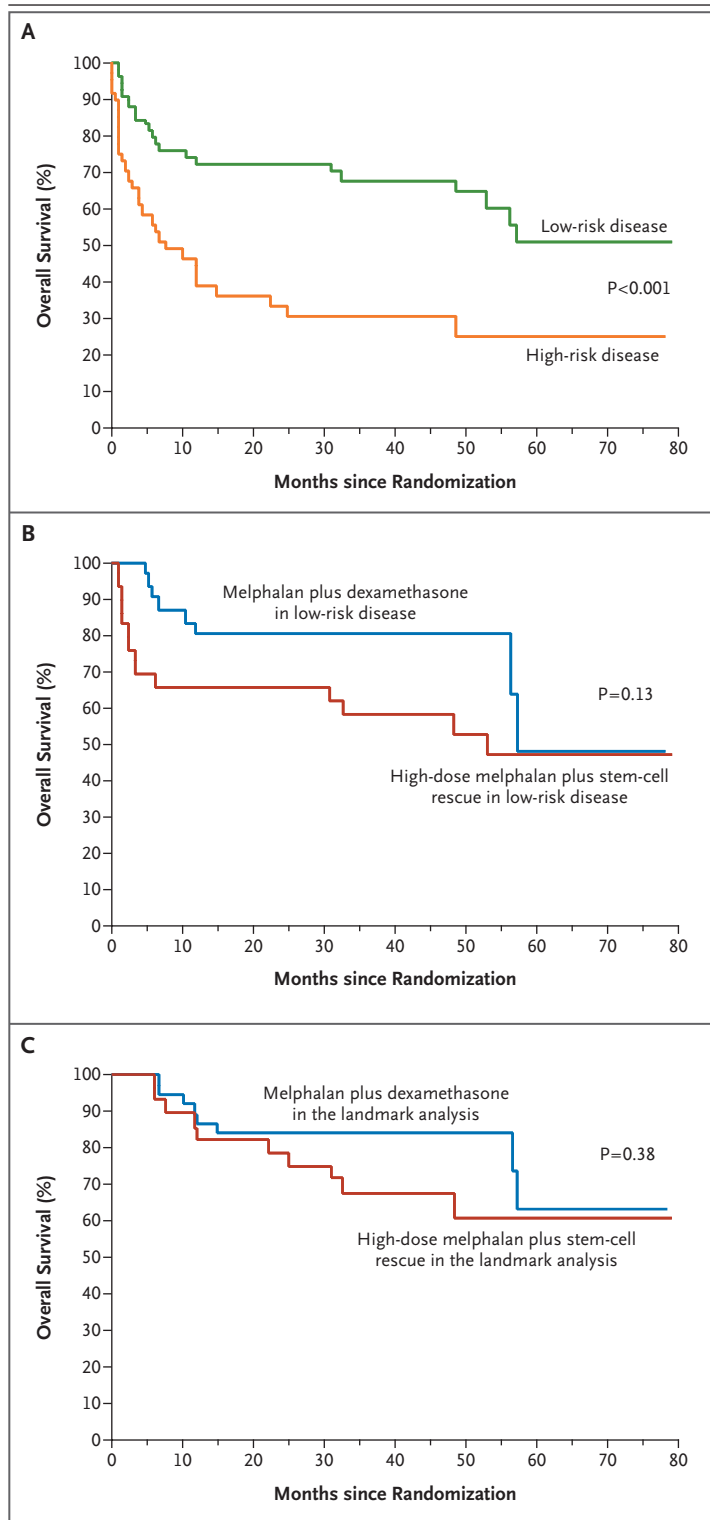
Figure 3. Survival According to Risk Group, According to the Treatment Group among Patients with Low-Risk Disease, and According to the Treatment Group in the Landmark Analysis.

Panel A shows survival according to disease severity. A total of 59 patients were at low risk for an adverse outcome of intensive treatment, and 41 were at high risk. Panel B shows survival according to treatment group in the 59 patients with low-risk disease. The 3-year survival in the group of patients assigned to melphalan plus dexamethasone was 80%, and in the group of patients assigned to high-dose melphalan it was 58%. Panel C shows survival according to treatment group in the landmark analysis. A total of 37 patients were assigned to melphalan plus dexamethasone, and 8 died. A total of 28 patients were assigned to high-dose melphalan, and 10 died.

melphalan (22.2 months) ($P=0.04$). Moreover, we found no significant difference in response rates between the two treatment groups. In a nonrandomized study with the use of the free light-chain assay, Lachmann et al. also found no difference in responses to high-dose chemotherapy or cytotoxic regimens such as vincristine, doxorubicin, and dexamethasone (VAD) or cyclophosphamide, vincristine, doxorubicin, and methylprednisolone (C-VAMP).¹²

More than two thirds of patients who received oral melphalan plus dexamethasone had durable hematologic responses. Similar results were reported in 2004 by Palladini et al., who treated 46 patients with melphalan plus dexamethasone and obtained a hematologic response rate of 67% and a clinical response rate of 48%.¹³ These rates are two to three times better than those obtained with the classic melphalan–prednisone combination mainly used in the case–control study in which intensive treatment was shown to offer better survival.⁷

One explanation for the relatively poor results with high-dose melphalan in our study is the high mortality rate before and after such intensive treatment. Most patients were treated in the same hospital where amyloidosis was diagnosed, and the median time from diagnosis to randomization was only 48 days for the two groups combined. Treatment in the same center would tend to limit the selection bias that may occur when patients are treated in tertiary referral centers, where patients who die rapidly after diagnosis cannot be treated.¹⁴ Because of the time required to collect stem cells and arrange hospitalization for treatment with high-dose melphalan, the delay before initiation of therapy was about 1 month longer in



the group assigned to receive high-dose melphalan than in the group assigned to receive melphalan plus dexamethasone. This delay also contributed, along with the toxic effects of the procedure,

to the higher number of early deaths in the group assigned to receive high-dose melphalan.

The treatment-related mortality rate after high-dose melphalan was higher in our multicenter study (24%) than in single-center studies of intensive treatment.^{4,5} However, it was similar to that observed in two other multicenter series: 25% among 114 patients treated in 50 U.S. centers¹⁵ and 23% among 92 patients treated in 31 British centers.¹⁶ Thus, our results are representative of those obtained with intensive treatment for AL amyloidosis in multicenter trials, even if the treatment-related mortality rate is reduced by strict patient selection.¹⁷ The toxic effects of G-CSF in patients with AL amyloidosis should be emphasized, since four of our patients died while receiving G-CSF.¹⁸

Our inclusion criteria were not as stringent as those used in large North American centers.^{4,19} To take into account the possible enrollment of patients with advanced disease, resulting in a disadvantage for the group assigned to receive high-dose melphalan, we stratified the patients according to whether they had low-risk or high-risk disease, using the criteria defined by Dispenzieri et al.⁶ Patients with high-risk disease in the two treatment groups had similarly poor outcomes, underlining the need for new treatments for these patients. Patients with low-risk disease are usually considered to be good candidates for intensive

treatment. Among such patients in our study, survival did not differ significantly between the two groups.

To reduce the influence of early treatment-related deaths on the survival analysis, we performed a landmark analysis that included only patients who survived for more than 6 months after randomization and who received their assigned treatment. This analysis also showed no advantage of high-dose melphalan as compared with melphalan plus dexamethasone (Fig. 3C).

In conclusion, this trial shows that high-dose melphalan is not superior to melphalan plus dexamethasone in patients with AL amyloidosis. A trial comparing the two treatments in a tertiary referral center, where the treatment-related mortality rate is likely to be lower, may have different results.

Presented in part at the 47th annual meeting of the American Society of Hematology, Atlanta, December 2005, and the 39th annual meeting of the American Society of Nephrology, San Diego, CA, November 2006.

Supported by Direction de la Recherche Clinique, Centre Hospitalier Universitaire, Limoges, and by grants from the Programme Hospitalier de Recherche Clinique and Limousin Association pour la Recherche en Hématologie Clinique.

No potential conflict of interest relevant to this article was reported.

We thank Fabienne Auroy, Abdeslam Bentaleb, Sandrine Naturel, and Valérie Pradel in Limoges and Claire Aguilar and Maria Basile in Paris for their excellent data monitoring and Benoît Marin from the Department of Clinical Research and Biostatistics in Limoges for his contribution to the statistical analysis.

APPENDIX

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