

ORIGINAL ARTICLE

## Single versus Double Autologous Stem-Cell Transplantation for Multiple Myeloma

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### ABSTRACT

#### BACKGROUND

We conducted a randomized trial of the treatment of multiple myeloma with high-dose chemotherapy followed by either one or two successive autologous stem-cell transplantations.

#### METHODS

At the time of diagnosis, 399 previously untreated patients under the age of 60 years were randomly assigned to receive a single or double transplant.

#### RESULTS

A complete or a very good partial response was achieved by 42 percent of patients in the single-transplant group and 50 percent of patients in the double-transplant group ( $P=0.10$ ). The probability of surviving event-free for seven years after the diagnosis was 10 percent in the single-transplant group and 20 percent in the double-transplant group ( $P=0.03$ ). The estimated overall seven-year survival rate was 21 percent in the single-transplant group and 42 percent in the double-transplant group ( $P=0.01$ ). Among patients who did not have a very good partial response within three months after one transplantation, the probability of surviving seven years was 11 percent in the single-transplant group and 43 percent in the double-transplant group ( $P<0.001$ ). Four factors were significantly related to survival: base-line serum levels of  $\beta_2$ -microglobulin ( $P<0.01$ ) and lactate dehydrogenase ( $P<0.01$ ), age ( $P<0.05$ ), and treatment group ( $P<0.01$ ).

#### CONCLUSIONS

As compared with a single autologous stem-cell transplantation after high-dose chemotherapy, double transplantation improves overall survival among patients with myeloma, especially those who do not have a very good partial response after undergoing one transplantation.

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**T**HE FAILURE OF CONVENTIONAL chemotherapy to improve the outlook in multiple myeloma<sup>1</sup> has led to the treatment of this disease with high-dose chemotherapy plus autologous stem-cell transplantation. Promising results have been obtained in pilot studies,<sup>2,3</sup> and randomized trials comparing autologous stem-cell transplantation with conventional chemotherapy in patients with newly diagnosed myeloma have been reported.<sup>4-8</sup> These studies demonstrated the superiority of autologous stem-cell transplantation over conventional treatment in terms of the response rate and event-free survival, but the effects on overall survival were unclear. A survival benefit was observed in French and British trials,<sup>4,5</sup> but not in others,<sup>6-8</sup> in part because stem-cell transplantation was used as salvage therapy after the failure of conventional chemotherapy. Thus, stem-cell transplantation is recommended for young patients with multiple myeloma as part of the initial therapy or at the time of disease progression.<sup>9</sup> However, the median duration of response after this procedure does not exceed three years, and almost all patients ultimately relapse.

To prolong the duration of response, double-intensive therapy, in which two successive autologous stem-cell transplantations are performed, has been evaluated in high-risk patients.<sup>10</sup> In a trial conducted almost 10 years ago, up to 73 percent of patients were able to tolerate double-intensive treatment, and the rate of complete response increased from 24 percent after the first transplantation to 43 percent after the second.<sup>11</sup> This report encouraged the use of double transplantation in young patients with myeloma,<sup>12,13</sup> but selection bias hindered a direct comparison of double and single transplantations. In 1994, we began a trial designed to make such a comparison.

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## METHODS

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### ELIGIBILITY

Patients less than 60 years of age who had Durie-Salmon stage I (one bone lesion), II, or III myeloma were eligible. The criteria for exclusion were prior treatment for myeloma, another cancer, abnormal cardiac function (indicated by a systolic ejection fraction less than 50 percent), chronic respiratory disease (indicated by a vital capacity or carbon monoxide diffusing capacity less than 50 percent of predicted), abnormal liver function (indicated by a serum bilirubin level more than 2 mg per deciliter

[35  $\mu$ mol per liter] or an alanine aminotransferase or aspartate aminotransferase level more than four times the upper limit of normal), and psychiatric disease. Between October 1994 and March 1997, 403 patients from 45 centers were enrolled. Four patients were excluded: one was older than 60 years of age, and three had primary plasma-cell leukemia. A total of 399 patients were evaluated. The study was approved by the institutional ethics committees, and the patients gave written informed consent.

### STUDY PROTOCOL

#### *Initial Randomization*

Patients were randomly assigned at the time of diagnosis to receive one or two autologous stem-cell transplants. The sequence of randomization was determined by the coordinating center (in Toulouse, France), which made the treatment assignment by telephone after each patient's eligibility was confirmed.

#### *Initial Chemotherapy*

In each group, patients were initially treated with a continuous intravenous infusion of 0.4 mg of vincristine per square meter of body-surface area and 9 mg of doxorubicin per square meter over a 24-hour period for four days, with 40 mg of oral dexamethasone per day on days 1 through 4 (the VAD regimen). Three or four cycles of VAD were administered at three-week intervals.

#### *Collection of Autologous Stem Cells*

After initial chemotherapy, patients with a performance status below World Health Organization grade 3 and a serum creatinine level of less than 1.7 mg per deciliter (150  $\mu$ mol per liter) underwent stem-cell collection. The source of stem cells (bone marrow or blood collected after the infusion of granulocyte colony-stimulating factor) was allocated according to a second randomization procedure at the time of stem-cell collection. A minimum of 2 million CD34+ cells per kilogram of body weight per transplantation was collected.

#### *Stem-Cell Transplantation*

In the group that received a single transplant, the preparative regimen was melphalan (140 mg per square meter) and total-body irradiation (8 Gy delivered in four fractions over a period of four days). In the group that received a double transplant, patients received the first transplant after preparation with melphalan alone (140 mg per square meter).

Melphalan and the same dose of total-body irradiation as the single-transplant group received were given before the second transplantation.

#### Maintenance Treatment with Interferon Alfa

After transplantation in each group, treatment with interferon alfa was administered three times a week at a dose of 3 million U. Interferon alfa was started after hematologic reconstitution.

#### CRITERIA FOR A RESPONSE

The response criteria of the European Group for Blood and Marrow Transplantation,<sup>14</sup> proposed in 1998, were not used in this study, which was initiated in 1994. A complete response was defined as the lack of detectable paraprotein by serum and urine electrophoresis and 5 percent or fewer plasma cells with normal morphologic features in a bone marrow aspirate.<sup>4</sup> A very good partial response was defined as a 90 percent decrease in the serum paraprotein level; a partial response was defined as a 50 percent decrease in the paraprotein level or a 90 percent decrease in the level of Bence Jones protein (including patients with Bence Jones protein alone) or both; a minimal response was defined as a 25 percent decrease in the paraprotein level; stable disease was defined as no change in the paraprotein level; progressive disease was defined as a 25 percent increase in the paraprotein level after two cycles of the initial chemotherapy; and a relapse was defined as the reappearance of paraprotein, the recurrence of bone marrow infiltration, or both in a patient who had had a complete response and as a 50 percent increase above the plateau level of paraprotein in two samples obtained four weeks apart in a patient who had had a response.

#### STATISTICAL ANALYSIS

The proportions of patients with a given characteristic were compared with the use of the chi-square test or Fisher's exact test. Differences in the means of continuous measurements were tested with the use of Student's *t*-test and checked with the use of the Mann-Whitney *U* test. All tests were two-tailed. The duration of event-free survival was calculated for all patients from the date of randomization to the time of progression, relapse, or death. The duration of relapse-free survival was calculated for patients who had at least a minimal response, from the date of randomization to the date of progression. Kaplan-Meier curves for event-free survival, relapse-free survival, and overall survival were plotted and compared with the use of the log-rank test. Prognos-

**Table 1. Base-Line Characteristics of the Patients According to Treatment Group.\***

Characteristic	Single-Transplant Group (N=199)	Double-Transplant Group (N=200)	All Patients (N=399)
Sex (no. of patients)			
Male	112	111	223
Female	87	89	176
Age (yr)	52±6	52±6	52±6
Durie-Salmon stage (no. of patients)			
I	17	14	31
II	23	31	54
III	159	155	314
M component (no. of patients)			
IgG	119	118	237
IgA	39	40	79
Bence Jones protein	37	40	77
IgD	4	2	6
Hemoglobin (g/dl)	10.7±2.3	10.7±2.1	10.7±2.2
Serum calcium (mmol/liter)	2.4±0.4	2.5±0.4	2.5±0.4
Serum albumin (g/liter)	39±7	38±6	38±6
Serum lactate dehydrogenase (IU/liter)	328±155	330±214	330±187
Serum creatinine (μmol/liter)	123±106	119±89	122±98
Bone marrow plasmacytosis (% of cells)	37±25	38±26	38±26
Serum beta <sub>2</sub> -microglobulin (mg/liter)	5±6	5±9	5±8
Serum C-reactive protein (mg/liter)	12±26	15±27	14±26

\* Plus-minus values are means ±SD. To convert values for calcium to milligrams per deciliter, divide by 0.250. To convert values for creatinine to milligrams per deciliter, divide by 88.4.

**Table 2. Response Rates.\***

Variable	Single-Transplant Group	Double-Transplant Group	P Value
	<i>no. of patients (%)</i>		
Completed VAD regimen	199	200	
Complete or very good partial response	25 (13)	23 (12)	0.90
Underwent 1 transplantation	170 (13)	177	
Complete or very good partial response within 3 mo	81 (48)	46 (26)	0.001
Actually received assigned therapy†	170	156	
Complete or very good partial response	84 (49)	99 (63)	0.01
Included in intention-to-treat analysis†	199	200	0.10
Complete or very good partial response	84 (42)	99 (50)	
Partial response	83 (42)	76 (38)	
Minimal response	15 (8)	12 (6)	
Progressive disease	17 (8)	13 (6)	

\* VAD denotes vincristine, doxorubicin, and dexamethasone.

† The maximal response is shown.

tic factors for survival were determined by means of the Cox proportional-hazards model for covariate analysis. The objective was to compare the two treatment groups with respect to the rates of complete response. A minimum of 180 randomized patients was required in each group to ensure that the study had a power of 95 percent to determine whether the true rates of complete response were 25 percent in the single-transplant group and 45 percent in the double-transplant group, given a significance level of 5 percent. The study was completed after 403 patients were enrolled. All patients who underwent randomization were studied in their assigned treatment groups.

RESULTS

BASE-LINE CHARACTERISTICS

Table 1 shows the base-line characteristics of the 399 patients. There were no significant differences between the two treatment groups.

COMPLETION OF ASSIGNED THERAPY

In the single-transplant group, 85 percent of patients underwent transplantation after a median

of 3 cycles of VAD (range, 3 to 6), and 57 percent of patients received interferon alfa for a median of 10 months (range, 4 to 35). A protocol violation, whether instituted by a physician or a patient, was the main reason for patients' not receiving interferon. In the double-transplant group, 88 percent of patients underwent the first transplantation after a median of 3 cycles of VAD (range, 3 to 6), and 78 percent underwent the second transplantation. The median time from the first to the second transplantation was 2.5 months (range, 2 to 7). In this group, 49 percent of patients received interferon for a median of 11 months (range, 5 to 30).

RESPONSE RATE

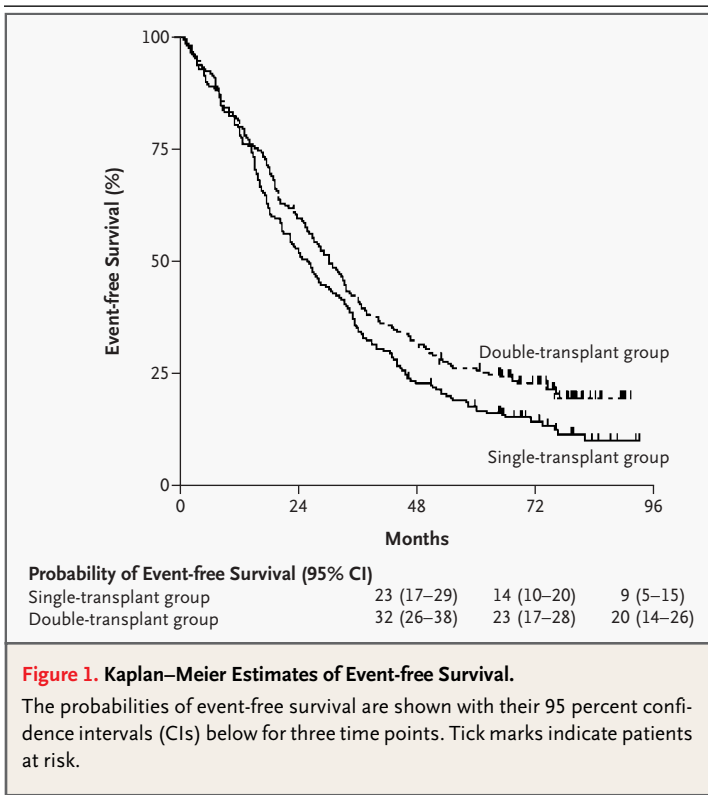
Table 2 shows the response rates at each step of the study. Within three months after preparative treatment with melphalan plus total-body irradiation and autologous stem-cell transplantation, 48 percent of patients in the single-transplant group had a complete or very good partial response, as compared with 26 percent of patients in the double-transplant group, who received their first transplant after treatment with melphalan alone (P=0.001).

The overall rates of complete or very good partial response for patients who actually received a single or a double transplant were 49 percent and 63 percent, respectively (P=0.01). However, when the results were analyzed on an intention-to-treat basis, the response rates in the two groups did not differ significantly (42 percent in the single-transplant group and 50 percent in the double-transplant group; P=0.10).

EVENT-FREE, RELAPSE-FREE, AND OVERALL SURVIVAL

In the single-transplant group, the median follow-up was 75 months (range, 51 to 93) from the time of randomization. The median durations of event-free, relapse-free, and overall survival were 25, 29, and 48 months, respectively. The probabilities of event-free, relapse-free, and overall survival seven years after the diagnosis were 10 percent (Fig. 1), 13 percent, and 21 percent (Fig. 2), respectively. Of the 143 deaths in this group, 124 were attributed to myeloma, 5 to the toxic effects of VAD (sepsis), 3 to the toxic effects of transplantation (sepsis), 9 to cardiovascular or thromboembolic disease, 1 to a brain tumor, and 1 to suicide.

In the double-transplant group, the median follow-up was 75 months (range, 36 to 93) from the time of randomization. The median durations of



**Figure 1. Kaplan-Meier Estimates of Event-free Survival.**  
The probabilities of event-free survival are shown with their 95 percent confidence intervals (CIs) below for three time points. Tick marks indicate patients at risk.

event-free, relapse-free, and overall survival were 30, 36, and 58 months, respectively. The probabilities of event-free, relapse-free, and overall survival seven years after the diagnosis were 20 percent (Fig. 1), 23 percent, and 42 percent (Fig. 2), respectively. Of the 113 deaths in this group, 95 were attributed to myeloma, 5 to the toxic effects of VAD (sepsis), 7 to the toxic effects of transplantation (sepsis), 4 to cardiovascular or thromboembolic disease, 1 to colon cancer, and 1 to an unknown cause. As compared with single transplantation, double transplantation improved event-free survival ( $P=0.03$ ) (Fig. 1), relapse-free survival ( $P<0.01$ ), and overall survival ( $P=0.01$ ) (Fig. 2).

#### PROGNOSTIC FACTORS FOR OVERALL SURVIVAL

In a multivariate analysis of all 399 patients, overall survival was significantly related to base-line serum levels of beta<sub>2</sub>-microglobulin ( $P<0.01$ ) and lactate dehydrogenase ( $P<0.01$ ), age ( $P<0.05$ ), and treatment assignment ( $P<0.01$ ). To assess the response to treatment as one of the variables that affected survival, we analyzed the group of 346 patients who survived more than one year after diagnosis (three months after the end of treatment). In a multivariate analysis, survival was related to the maximal response to treatment ( $P<0.001$ ), age ( $P=0.05$ ), base-line serum lactate dehydrogenase level ( $P=0.03$ ), and treatment assignment ( $P=0.01$ ). The overall survival among patients with a complete response who had a negative result when tested for myeloma protein by immunofixation (which is a more sensitive method of detecting paraproteins than standard electrophoresis) was similar to that among such patients with detectable levels of myeloma protein (data not shown).

We compared overall survival according to the treatment group in different subgroups of patients. As compared with a single transplantation, double transplantation prolonged survival within each of the following subgroups: patients with beta<sub>2</sub>-microglobulin levels of 3 mg per liter or less, patients with beta<sub>2</sub>-microglobulin levels of more than 3 mg per liter, patients with lactate dehydrogenase levels of 330 IU or less, patients with lactate dehydrogenase levels of more than 330 IU, patients with Durie-Salmon stage I or II disease, patients with Durie-Salmon stage III disease, patients 50 years of age or younger, and those older than 50 years of age.

The effect of a single or a double transplantation on overall survival differed according to the response achieved three months after one transplantation.

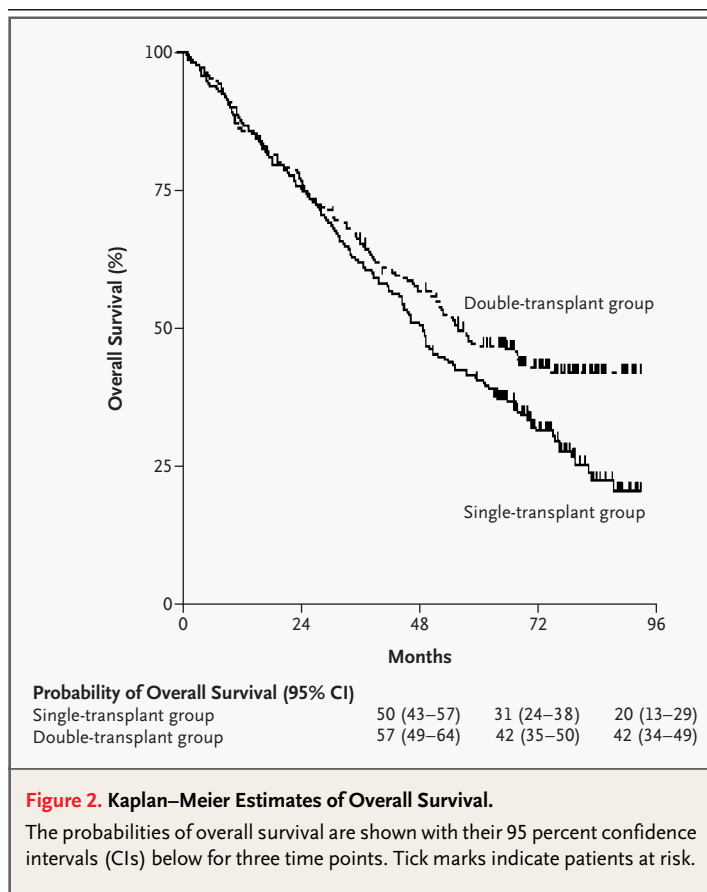
Patients who did not have at least a very good partial response after the first procedure had a significant benefit from the second transplantation. The rates of survival at seven years were 11 percent in the single-transplant group and 43 percent in the double-transplant group ( $P<0.001$ ) (Fig. 3B). Patients who had at least a very good partial response did not benefit significantly from the second transplantation ( $P=0.70$ ) (Fig. 3A).

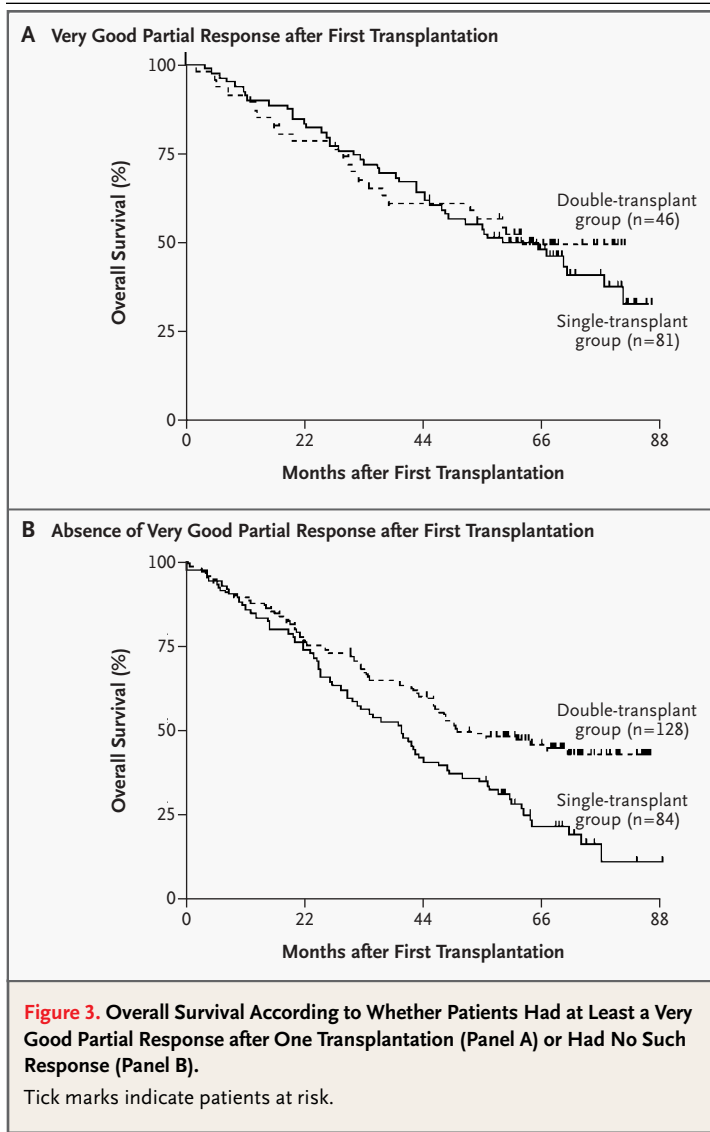
#### TREATMENT-RELATED TOXICITY

The hematopoietic reconstitution was similar in the two groups. There were 8 (4 percent) treatment-related deaths in the single-transplant group and 12 (6 percent) in the double-transplant group ( $P=0.40$ ) (Table 3).

#### SALVAGE THERAPY

In the single-transplant group, 148 patients had a relapse: 13 received no salvage therapy, whereas 135 received conventional chemotherapy; 33 underwent another stem-cell transplantation, and 23 received





thalidomide. With a median follow-up of 29 months from the time of relapse, the probability of survival 2 years after relapse was 36 percent.

In the double-transplant group, 129 patients relapsed: 12 received no salvage therapy, whereas 117 received conventional chemotherapy; 34 underwent another stem-cell transplantation, and 25 received thalidomide. With a median follow-up of 30 months from the time of relapse, the probability of survival 2 years after relapse was 36 percent.

#### SOURCE OF STEM CELLS

The time to hematopoietic reconstitution after high-dose therapy was faster after the receipt of a periph-

eral-blood graft than a bone marrow graft (data not shown). There were no significant differences in terms of the response rate, event-free survival, or overall survival according to the source of stem cells.

#### DISCUSSION

We found that two successive autologous stem-cell transplantations, each preceded by high-dose chemotherapy, improved overall survival among patients with myeloma more than did a single transplantation after high-dose chemotherapy. The probability of surviving seven years after the diagnosis was 42 percent in the double-transplant group and 21 percent in the single-transplant group ( $P=0.01$ ). This survival benefit required a minimal follow-up of five years after diagnosis to reach a statistically significant level. In other recent studies of double transplantation in patients with myeloma, the follow-up ranged from 30 to 40 months, which we believe is not a sufficient period from which to draw definite conclusions.<sup>15-17</sup>

We previously reported that a complete response after high-dose chemotherapy plus a single transplantation was the most important prognostic factor for survival among patients with myeloma.<sup>18</sup> In the current trial, 49 percent of patients who received a single transplant had a complete or a very good partial response, as compared with 63 percent after two transplantations ( $P=0.01$ ). However, when the results were analyzed on an intention-to-treat basis, the response rates in the two groups did not differ significantly, and therefore, the quality of these responses cannot explain the difference in survival. Instead, it appears that double transplantation improves survival by prolonging the duration of the response. The probability of surviving free of relapse for seven years after the diagnosis was 13 percent in the single-transplant group and 23 percent in the double-transplant group ( $P<0.01$ ), with similar survival rates after relapse in the two groups. The reasons for the longer duration of response in the double-transplant group are unknown. The suppression of either residual tumor cells or non-specific damage to the marrow microenvironment, which is necessary for tumor growth, could be involved.

One objective of our trial was to evaluate the feasibility and toxic effects of double transplantation. Among the patients enrolled in the double-transplant group, 22 percent could not receive their as-

signed therapy. The most common reasons were poor performance status and poor stem-cell collection owing to an insufficient response after the initial VAD treatment. Treatment with a combination of VAD and proteasome inhibitors,<sup>19</sup> thalidomide,<sup>20</sup> or its immunomodulatory analogues<sup>21</sup> might improve the initial response rate and lower the exclusion rate. The risk of life-threatening toxic effects due to double transplantation was a major concern. However, the hematopoietic reconstitution was similar after one or two transplantations, and the rates of death caused by toxic effects did not differ significantly between the two groups. We used the combination of high-dose melphalan and total-body irradiation, long considered the standard conditioning regimen before transplantation. We recently reported that high-dose melphalan alone (200 mg per square meter) was less toxic and associated with longer survival than high-dose melphalan plus total-body irradiation.<sup>22</sup> Thus, toxicity could be diminished and survival might be improved if recipients of double transplants received melphalan alone.

The morbidity and costs of double transplantations justify the use of an approach in which patients who could benefit the most from this treatment are selected. Our results indicate that double transplantation could benefit patients who do not have a very good partial response within three months after undergoing a single transplantation. Indeed, the seven-year survival rate among such patients was 11 percent after one transplantation in the single-transplant group and 43 percent in the double-transplant group ( $P < 0.001$ ). Another strategy for patients with a very good partial response after undergoing one transplantation, recently proposed by the Royal Marsden group, is maintenance chemotherapy, with a second transplantation at the time of disease progression.<sup>23</sup> We prepared recipients of the first transplant with 140 mg of melphalan per square meter; the use of a dose of 200 mg per square meter might improve the rates of very good partial response, thereby reducing the need for a second transplantation.

Although our trial demonstrates that double

**Table 3. Treatment-Related Toxicity.\***

Adverse Effect	Single-Transplant Group	Double-Transplant Group
<b>Related to initial chemotherapy</b>		
No. of patients	199	200
No. of treatment-related deaths	5	5
<b>Related to conditioning regimen</b>		
Melphalan alone		
No. of patients	—	177
Duration of neutropenia (<500 white cells/mm <sup>3</sup> ) — days	—	8±4
Duration of thrombocytopenia (<50,000 platelets/mm <sup>3</sup> ) — days	—	9±7
No. of platelet transfusions	—	2±5
No. of treatment-related deaths	—	3
Melphalan plus total-body irradiation		
No. of patients	170	156
Duration of neutropenia (<500 white cells/mm <sup>3</sup> ) — days	10±4	10±3
Duration of thrombocytopenia (<50,000 platelets/mm <sup>3</sup> ) — days	13±10	14±19
No. of platelet transfusions	4±5	5±5
No. of treatment-related deaths	3	4
Treatment-related deaths — no. (%)	8 (4)	12 (6)

\* Plus-minus values are means ±SD. There were no significant differences between groups.

transplantation improves overall survival among patients with myeloma, the absence of a plateau in the curve for event-free survival justifies the development of new strategies to control this disease. The use of thalidomide and its more effective immunomodulatory analogues, proteasome inhibitors, plasma-cell-directed monoclonal antibodies, vaccine therapy, and inhibitors of bone marrow resorption may modify the approach to the treatment of this disease.

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#### APPENDIX

The following centers and investigators from the IFM participated in this study: France — Amiens, Hôpital Sud (B. Desablens); Angers, Centre Hospitalier Régional et Universitaire (N. Ifrah, M. Dib); Annecy, Centre Hospitalier (B. Corront, C. Martin); Avignon, Hôpital Henri Duffaut (S. Rossanino, G. Lepeu); Bayonne, Centre Hospitalier (M. Renoux, F. Bauduer); Besançon, Hôpital Jean Minjoz (J.Y. Cahn, L. Voillat); Blois, Centre Hospitalier (D. Rodon); Bobigny, Hôpital Avicenne (P. Casassus); Bordeaux, Hôpital du Haut-Lévêque (G. Marit, J.M. Boiron); Bourges, Centre Hospitalier (H. Orfeuvre); Brest, Hôpital Augustin Morvan (C. Autrand); Châlons-sur-Saône, Centre Hospitalier (B. Salles); Cholet, Polyclinique du Parc (D. Zannetti); Clermont-Ferrand, Hôpital Hôtel Dieu (A.C. Fouilhoux); Compiègne, Centre Hospitalier (D. Veysier); Dijon, Centre Hospitalier du Bocage (D. Caillot); Grenoble, Hôpital Albert Michallon (J.J. Sotto, B. Pegourié, L. Molina); La

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**CORRECTION**

**Single versus Double Autologous Stem-Cell Transplantation for Multiple Myeloma**

Single versus Double Autologous Stem-Cell Transplantation for Multiple Myeloma . On pages 2498, 2499, and 2500, the legends for Figures 1, 2, and 3, respectively, should have stated, "Tick marks indicate patients whose data were censored," rather than "Tick marks indicate patients at risk," as printed.