

Comparison of High-Dose Melphalan with a More Intensive Regimen of Thiotepa, Busulfan, and Cyclophosphamide for Patients with Multiple Myeloma

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BACKGROUND. High-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) as part of the initial treatment regimen improves progression-free survival (PFS) and overall survival (OS) for patients with multiple myeloma. The optimal preparative regimen for patients with multiple myeloma has yet to be defined. In the current study, the authors compared the outcomes associated with high-dose melphalan (HDM) and a more intensive regimen of thiotepa, busulfan, and cyclophosphamide (TBC) in patients with multiple myeloma.

METHODS. One hundred eighty-six patients with newly diagnosed multiple myeloma (median age, 51 years) received HDC with ASCT for consolidation of first remission ($n = 108$) or for treatment of primary refractory disease ($n = 78$). Seventy patients had a large tumor mass at the time of diagnosis. The preparative regimen consisted of TBC for 97 patients and HDM for 89 patients. Patients in the TBC group were younger and had more advanced disease stage at diagnosis and at the time of ASCT compared with patients in the HDM group.

RESULTS. The response rates (complete response [CR] and partial response [PR]) were similar in the TBC group (overall response rate, 66%; CR rate, 17%; PR rate, 49%) and the HDM group (overall response rate, 69%; CR rate, 28%; PR rate, 41%). PFS and OS were similar in both groups. A proportional hazards regression model revealed that Durie-Salmon disease stage at diagnosis and having received three or more previous treatment regimens were the only factors that predicted PFS; the type of preparative regimen did not influence outcome.

CONCLUSIONS. The results of the current study indicate that the use of a more intensive regimen did not improve results compared with HDM in patients with multiple myeloma. HDM should continue to be considered the standard preparative regimen for patients with myeloma. *Cancer* 2004;100:2607-12.

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It has been shown that high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) increases the rates of overall response, survival, and event free survival when administered as part of initial therapy for patients with multiple myeloma.¹ The effects of the preparative regimen on transplantation outcomes in patients with myeloma have been studied, but there is no consensus regarding which is the best conditioning regimen. High-dose melphalan at a dose of 200 mg/m² (HDM) is considered by most experts to be the standard conditioning regimen.²⁻⁴ HDM is well tolerated and can be

TABLE 1
Patient Characteristics by Treatment Group

Characteristic	Total	TBC	HDM	P value
No. of patients	186	97	89	—
Age $\geq$ 55 yrs (%)	52	38	65	< 0.0001
Durie-Salmon Stage III ^a	63	70	55	0.03
High tumor mass (%) ^a	38	44	30	0.03
LDH > 618 U/L (%) ^a	24	33	26	0.61
β_2 -microglobulin > 2.0 mg/L (%) ^a	44	38	49	0.12
Median serum paraprotein (gm/Lt) ^a	1.25	1.7	0.5	< 0.0001
< 12 mos to ASCT (%)	78	74	82	0.2
Three or more previous regimens (%)	34	41	26	0.03
Primary refractory disease at the time of ASCT (%)	42	51	33	0.01

TBC: thiotepa, busulfan, and cyclophosphamide; HDM: high-dose melphalan; LDH: lactate dehydrogenase; U: units; ASCT: autologous stem cell transplantation.

^a Note: These characteristics refer to the time of initial diagnosis.

administered safely in an outpatient setting. Moreau et al. recently published the results of a French multicenter randomized study comparing outcomes after ASCT for patients who received HDM and patients who received melphalan at a dose of 140 mg/m² plus 8 grays (Gy) of total-body irradiation (TBI).⁵ Similar response rates and remission times with significantly improved overall survival and better tolerance indicated the superiority of the HDM regimen over combined chemoradiotherapy, thus establishing HDM as the *gold standard* with which other regimens should be compared. In the current study, we performed a retrospective analysis of patients with multiple myeloma who were treated either with HDM or with a more intensive regimen of thiotepa, busulfan, and cyclophosphamide (TBC) for consolidation of first remission or for treatment of refractory primary disease.

MATERIALS AND METHODS

Eligibility Criteria

The Department of Blood and Marrow Transplantation of the University of Texas M. D. Anderson Cancer Center (Houston, TX) maintains a complete database of all patients with multiple myeloma who have undergone ASCT. The current analysis was restricted to patients who underwent ASCT between May 30, 1991, and June 28, 2001. Patients were included in the study if they underwent ASCT for consolidation of a first remission or due to a lack of response to induction therapy (i.e., for treatment of refractory primary disease) and received either HDM or TBC. We excluded five patients who underwent ASCT after achieving complete remission prior to consolidative ASCT, because the achievement of complete remission was a study endpoint.⁶ One hundred eighty-six patients who fulfilled the study entry criteria were identified. All patients were treated according to institutional review

board (IRB)-approved protocols, and approval of the retrospective analysis also was obtained from the IRB. Ninety-seven patients (Group A) received a preparative regimen that consisted of combination TBC,⁷ and 89 patients (Group B) received HDM.

Patients and Disease Characteristics

Patient and disease characteristics are summarized in Table 1. In brief, the median patient age was 51 years (range, 31–71 years), and the median time from diagnosis to transplantation was 7.5 months ($\leq$ 12 months for 78% of patients). At the time of diagnosis, 117 patients had Durie-Salmon Stage III disease, and 70 patients had high tumor mass, which was defined by either a corrected serum calcium level > 11.5 mg/dL or a hemoglobin level < 8.5 g/dL.⁸ At the time of transplantation, 108 patients had disease that was in first remission, 78 patients had not achieved at least partial remission (i.e., they had refractory primary disease), and 63 patients already had received $\geq$ 3 treatment regimens. Patients had peripheral blood stem cells collected after chemotherapy ($n = 94$) or after granulocyte-colony-stimulating factor mobilization ($n = 92$).

ASCT Characteristics

Patients in Group A were conditioned with daily thiotepa 150 mg/m² administered intravenously for 3 days, busulfan 1 mg/kg administered orally or 0.8 mg/kg administered intravenously every 6 hours for 10 doses, and cyclophosphamide 60 mg/kg administered daily for 2 days.^{7,9} Patients in Group B received melphalan 100 mg/m² daily for 2 days (HDM).² All patients received standard post-ASCT supportive care, which included growth factor support, blood transfusions, and prophylactic or therapeutic antibiotics according to departmental guidelines at the time.

Outcomes

Engraftment was defined as the achievement of an absolute neutrophil count $> 0.5 \times 10^9/\text{L}$ for 3 consecutive days, and for the purposes of the analysis, platelet engraftment was defined as the achievement of platelet counts $> 50 \times 10^9/\text{L}$ without transfusion. A complete response (CR) was defined as the disappearance of the monoclonal protein, even on immunofixation analysis. A partial response (PR) was defined as a reduction of $> 50\%$ in serum paraprotein levels and/or a reduction of $> 90\%$ in urinary paraprotein levels for at least 6 weeks. The paraprotein levels measured immediately before HDC administration were considered to be baseline levels. For patients with nonsecretory myelomas, a reduction of $> 50\%$ in bone marrow plasma cells was considered indicative of a PR, while the observation of $< 5\%$ bone marrow plasma cells was considered indicative of a CR. Disease progression was defined by an increase of $> 25\%$ in serum or urinary paraprotein levels on at least 2 occasions, an increase in the number or size of osteolytic lesions, or the development of hypercalcemia. Patients who had achieved a CR were categorized as having progressive disease in all of the above scenarios and in the case of reappearance of a positive result on a serum or urine immunofixation test.¹⁰

Statistical Methods

The chi-square test and the Fisher exact test were used to compare categorical variables between the two treatment groups. The Wilcoxon rank-sum test was used to compare continuous variables between the two treatment groups. Remission and survival distributions were estimated using the method of Kaplan and Meier. The log-rank test was used to compare survival distributions between treatment arms and patient subgroups. Overall survival was defined as the time from transplantation (i.e., the date of peripheral blood stem cell infusion) to the date of death due to any cause. For the analysis of overall survival, patients who remained alive were censored at the date of their last follow-up. Progression-free survival (PFS) was defined as the time from transplantation to the time of disease progression or death due to any cause. For the analysis of PFS, patients who did not experience disease progression and who remained alive at the time of last follow-up were censored. CR duration was calculated as PFS minus the time to CR with respect to the same event that defined PFS. Backward-selection proportional hazards (Cox) regression analysis was used to evaluate the simultaneous effects of multiple patient characteristics on PFS. Although overall survival was an important outcome, multiple factors (e.g., the

number and type of postrecurrence therapy regimens received, patient characteristics during follow-up, etc.) confounded detailed inferences regarding this outcome. Consequently, Cox modeling was restricted to PFS. Statistical analyses were carried out using SAS software (SAS Inc., Cary, NC), and graphs were constructed using Splus software (Insightful Corporation, Seattle, WA).

RESULTS

Patient and Disease Characteristics

Table 1 shows that patients in Group A were younger and had more advanced disease stage at diagnosis; in addition, Group A had a greater percentage of heavily pretreated patients and patients with refractory primary disease. Because of our treatment protocol priorities, all patients in the HDM arm underwent ASCT after March 1998, whereas only 35% of patients in the TBC group underwent ASCT after that date.

Engraftment Data

All patients experienced recovery of neutrophil counts to $> 0.5 \times 10^9/\text{L}$ after a median of 10 days in both the TBC arm (Group A) and the HDM arm (Group B). Ten patients did not have platelet counts $\geq 50 \times 10^9/\text{L}$, including 9 patients in Group A and 1 patient in Group B. All other patients achieved platelet engraftment at median times of 14 days and 15 days after transplantation, respectively, in the HDM and TBC arms ($P = 0.002$).

Outcomes

Sixty-seven percent of patients ($n = 124$) responded to ASCT with either a CR ($n = 40$; 22%) or a PR ($n = 84$; 45%). The CR and PR rates were 16% and 50%, respectively, in Group A and 27% and 42%, respectively, in Group B. The difference in CR rates between the two treatment groups did not achieve statistical significance ($P = 0.08$). After controlling for the effects of disease status at the time of transplantation, differences in CR rates for Groups A and B also were not significant (odds ratio, 1.5; 95 confidence interval [CI], 0.7–3.1; $P = 0.31$). However, the time required to achieve a CR was significantly shorter in the HDM arm (Group B). Among patients who underwent ASCT for consolidation of first remission, 15 of 48 (31%) in Group A and 20 of 60 (33%) in Group B experienced conversion of their initial PR to a CR ($P = 0.8$). Among patients who underwent ASCT for refractory primary disease, 26 of 49 (53%) in Group A and 19 of 29 (66%) in Group B achieved a PR or a CR ($P = 0.28$). After median follow-up durations of 45 months in Group A and 17 months in Group B, 122 patients (66%) remained alive. Of the 64 patients who died, 14 (8%)

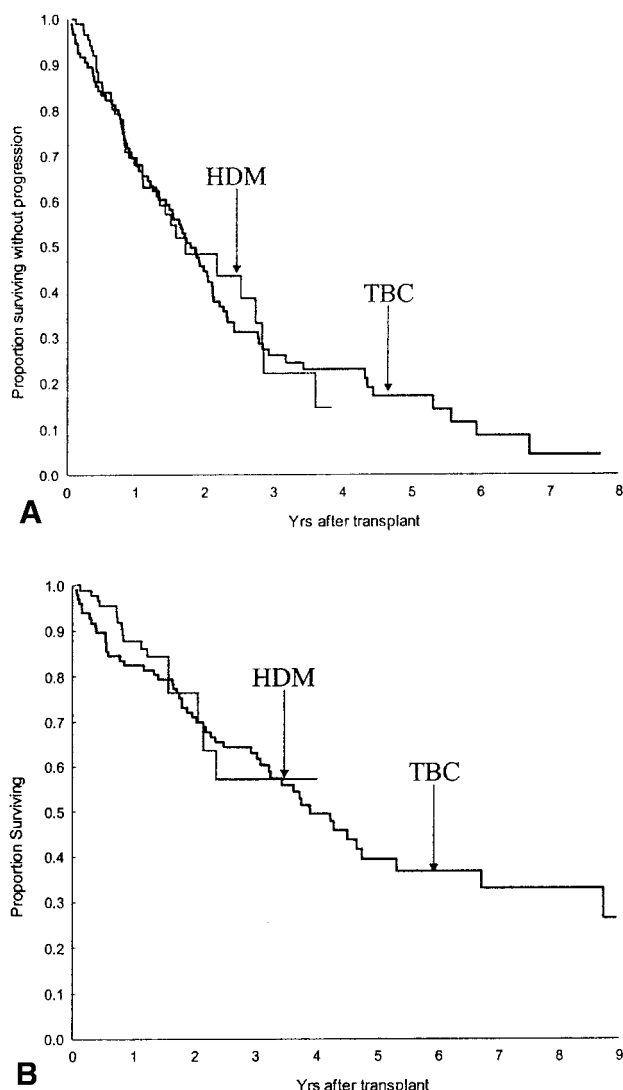


FIGURE 1. Similar (A) event-free survival and (B) overall survival in the high-dose melphalan (HDM) group and the thiotepa, busulfan, and cyclophosphamide (TBC) group.

died of causes other than disease progression, with 7 (4%) dying within 100 days after transplantation (6 patients in Group A and 1 patient in Group B; $P = 0.12$; Fisher exact test). Causes of death included infection ($n = 2$), multiorgan failure ($n = 3$), and hemorrhage ($n = 2$). The median overall survival for Group A was 46 months (95% CI, 38–64 months), and the median overall survival for Group B had not yet been reached at the time of the current analysis (Fig. 1A). Overall, 120 patients (65%) have developed progressive disease or died. The median PFS for all patients was 21 months (95% CI, 16–25 months) in Group A and 20 months (95% CI, 15–34 months) in Group B (Fig. 1B).

TABLE 2
Univariate Hazard Ratios for Progression-Free Survival by Patient, Disease, and Treatment Characteristics in 186 Patients with Myeloma Who Underwent Autologous Stem Cell Transplantation

Characteristic	HR (95% CI)	P value
Group A (vs. Group B)	0.99 (0.67–1.47)	0.97
Age ≥ 55 yrs	1.13 (0.79–1.63)	0.50
Stage III disease ^a	1.62 (1.09–2.4)	0.02
High tumor mass ^a	1.54 (1.08–2.22)	0.02
LDH > 618 U/L ^a	1.13 (0.73–1.73)	0.59
β_2 -microglobulin > 2.0 mg/L ^a	1.3 (0.90–1.86)	0.21
Serum paraprotein (continuous variable) ^a	1.04 (0.94–1.15)	0.47
Mos to ASCT (continuous variable)	0.92 (0.59–1.42)	0.71
Three or more previous regimens	1.56 (1.08–2.22)	0.02
Status at ASCT: first remission	0.79 (0.55–1.13)	0.20

HR: hazard ratio; 95% CI: 95% confidence interval; LDH: lactate dehydrogenase; ASCT: autologous stem cell transplantation.

^a Note: These characteristics refer to the time of initial diagnosis.

Association of Patient and Treatment Characteristics with PFS

Table 2 lists hazard ratios for disease progression according to patient, disease, and treatment characteristics. Higher disease stage at diagnosis (i.e., Durie–Salmon Stage III or high tumor mass) and having previously received three or more treatment regimens at the time of ASCT were found to be associated with statistically significantly shorter PFS. Patients in Groups A and B had similar PFS results. It should be noted that patients who underwent ASCT for the treatment of refractory disease did not have significantly shorter PFS compared with patients who underwent ASCT for consolidation of first remission.

Multivariate Cox regression analyses were used to adjust for differences in the distributions of the patient characteristics identified above, to evaluate the interdependence among patient characteristics, to identify a parsimonious prognostic model for PFS, and to estimate the effects of the preparative regimen on PFS. Each of the modeling steps adjusted for imbalances in the patient characteristics modeled. In a model that included all variables regardless of their significance, the number of prior treatments and Durie–Salmon Stage III disease at diagnosis were the only significant prognostic variables after adjusting for the effects of all other variables. The hazard ratio was 1.88 for patients who had Durie–Salmon Stage III disease ($P = 0.02$) and 1.68 for patients who had ≥ 3 prior treatments ($P = 0.03$). Treatment group did not affect PFS significantly. Using the method of backward-elimination proportional hazards regression, these two variables (number of prior treatments and disease stage) remained the only significant prognostic factors for

TABLE 3
Estimated Effect of Preparative Regimen on Progression-Free Survival After Adjustment for Significantly Prognostic Variables

Variable	HR (95% CI)	P value
Durie–Salmon Stage III	1.71 (1.14–2.54)	0.009
Three or more previous treatments	1.61 (1.13–2.39)	0.009
HDM as preparative regimen (Group A)	0.85 (0.57–1.28)	0.44

HR: hazard ratio; 95% CI: 95% confidence interval; HDM: high-dose melphalan.

PFS. Tumor mass, which had a strong univariate impact on PFS (Table 2), was not significant on multivariate analysis, probably due to the association between tumor mass at diagnosis and Durie–Salmon Stage III disease at diagnosis ($P < 0.0001$; chi-square test). Ninety-six percent of the 70 patients who had high tumor mass at diagnosis had Durie–Salmon Stage III disease, whereas only 43% of the 116 patients who had low tumor mass at diagnosis had Durie–Salmon Stage III disease. It is reasonable to assume that this strong association resulted in overlapping prognostic effects for these two variables. On multivariate analysis, Durie–Salmon stage had slightly more impact, and the additional independent effects of tumor mass were statistically nonsignificant. Finally, the estimated impact of the preparative regimen (Group A or Group B) on PFS, after adjustment for Durie–Salmon Stage III disease and the number of prior regimens, was equivocal ($P = 0.44$) (Table 3).

DISCUSSION

Multiple myeloma is one of the few hematologic malignancies for which HDC is accepted as frontline treatment.^{2,4} However, to our knowledge, all relevant studies have demonstrated that although HDC improves survival, most patients will develop progressive disease and eventually die as a result. Intensifying the preparative regimen would be a reasonable approach to maximizing cytoreduction and improving outcome. However, the optimal preparative regimen for patients with myeloma has not yet been defined. Is HDM enough, or can more intensive regimens potentially improve outcomes? At a time when new agents, such as thalidomide, thalidomide analogues, and proteasome inhibitors, that have considerably improved toxicity profiles are promising to change treatment priorities for patients with myeloma, it is important to optimize the safety and efficacy of HDC.¹¹

In our attempt to address this issue, we performed a retrospective analysis, reviewing outcomes of patients with myeloma who were treated with HDM or with a multiagent chemotherapeutic regimen (TBC) at

our institution. The current study included a large number of patients, but our results should be interpreted with caution, due to the limitations of retrospective studies. Patients in the current study had received a variety of induction regimens before undergoing ASCT and received a variety of maintenance treatments thereafter. Although this issue has not been clarified, we recently published a retrospective study indicating that the outcomes of autologous transplantation in patients with multiple myeloma were not affected by the type of induction regimen used.¹² Furthermore, there is no evidence that interferon alpha maintenance following ASCT prolongs survival.¹³ Because the current patient population was not assigned randomly into treatment groups, their pretransplantation characteristics had significant differences. The significantly older age of patients in the HDM group (median age, 55 years, compared with 49 years in the TBC group) may have had a negative effect on outcome. However, patients in the HDM group also had a significantly smaller probability of having advanced disease stage at diagnosis or refractory disease at the time of transplantation, and these factors represented a prognostic advantage. PFS was similar (~20 months) in both groups. Moreover, in the multivariate model, after adjustment for all other factors, there was not a significant association between the preparative regimen and PFS; in addition, we did not observe any significant effect on overall survival. Advanced disease stage at diagnosis and three or more treatment regimens before HDC treatment were the only significant factors for predicting PFS.

It is true that the TBC combination is more toxic than HDM alone. In the current report, we have stated that there was a difference (statistically nonsignificant) in 100-day mortality between the two groups that may indirectly indicate a difference in toxicity between the two regimens. However, the finding that most patients in Group A (TBC) received high-dose therapy early in the 1990s also indicates that differences in early mortality and/or toxicity may reflect differences in supportive care compared with patients in Group B (HDM), who received high-dose therapy later in the decade.

Randomized trials comparing HDM with melphalan plus TBI and retrospective studies have demonstrated the superiority of HDM in terms of tolerance and toxicity, with additional TBI providing no benefit with respect to long-term disease control.^{5,14–16} Thus, intensification of the preparative regimen has been attempted to improve autologous transplantation outcomes in patients with myeloma. Among the strategies for intensification, tandem transplantation,¹⁷ in-

tensified chemotherapy,^{9,16,18} and targeted skeletal radiotherapy¹⁹ have been explored.

Tandem transplantation may be associated with improved outcome, but a significant proportion of patients can never undergo the second transplantation. Thus, improving the results of single transplantation is essential. In a retrospective comparative study of 451 patients with myeloma who were treated with HDM, melphalan plus TBI, or melphalan plus busulfan (BuMel), no regimen was found to have a significant independent advantage in terms of PFS over any other regimen on multivariate analysis. In that report, PFS in the HDM group was 22 months, whereas PFS in the melphalan plus TBI group was 20 months, similar to the PFS durations reported in the French study and the current study. However, PFS in the BuMel group was significantly longer (32 months) on univariate analysis.¹⁶ Based on these limited data from the literature, it is reasonable to design randomized studies comparing HDM with combination chemotherapy regimens to optimize the outcomes of ASCT in patients with myeloma.

REFERENCES

1. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med*. 1996;335:91-97.
2. Barlogie B. High-dose therapy and innovative approaches to treatment of multiple myeloma. *Semin Hematol*. 2001;38:21-27.
3. Cunningham D, Paz-Ares L, Milan S, et al. High-dose melphalan and autologous bone marrow transplantation as consolidation in previously untreated myeloma. *J Clin Oncol*. 1994;12:759-763.
4. Harousseau J, Attal M. The role of stem cell transplantation in multiple myeloma. *Blood Rev*. 2002;16:245-253.
5. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m² melphalan and 8 Gy total body irradiation plus 140 mg/m² melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Franco-phone du Myelome 9502 randomized trial. *Blood*. 2002;99:731-735.
6. Alexanian R, Weber D, Giralt S, et al. Impact of complete remission with intensive therapy in patients with responsive multiple myeloma. *Bone Marrow Transplant*. 2001;27:1037-1043.
7. Shimoni A, Smith TL, Aleman A, et al. Thiotepa, busulfan, cyclophosphamide (TBC) and autologous hematopoietic transplantation: an intensive regimen for the treatment of multiple myeloma. *Bone Marrow Transplant*. 2001;27:821-828.
8. Alexanian R, Balcerzak S, Bonnet J, et al. Prognostic factors in multiple myeloma. *Cancer*. 1975;36:1192-1201.
9. Dimopoulos MA, Alexanian R, Przepiorka D, et al. Thiotepa, busulfan, and cyclophosphamide: a new preparative regimen for autologous marrow or blood stem cell transplantation in high-risk multiple myeloma. *Blood*. 1993;82:2324-2328.
10. Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol*. 1998;102:1115-1123.
11. Anderson KC, Kyle RA, Dalton WS, et al. Multiple myeloma: new insights and therapeutic approaches. *Hematology (Am Soc Hematol Educ Program)*. 2000:147-165.
12. Anagnostopoulos A, Aleman A, Yang Y, et al. Outcomes of autologous stem cell transplantation in patients with multiple myeloma who received dexamethasone-based nonmyelosuppressive induction therapy. *Bone Marrow Transplant*. 2004;33:623-628.
13. Cunningham D, Powles R, Malpas J, et al. A randomized trial of maintenance interferon following high-dose chemotherapy in multiple myeloma: long-term follow-up results. *Br J Haematol*. 1998;102:495-502.
14. Majolino I, Vignetti M, Meloni G, et al. Autologous transplantation in multiple myeloma: a GITMO retrospective analysis on 290 patients. Gruppo Italiano Trapianti di Midollo Osseo. *Haematologica*. 1999;84:844-852.
15. Björkstrand B, Svensson H, Goldschmidt H, et al. EBMT Registry results of autologous bone marrow and peripheral blood stem cell transplantation [abstract]. Presented at the VII International Multiple Myeloma Workshop, Stockholm, Sweden, September 1-5, 1999.
16. Lahuerta JJ, Martinez-Lopez J, Grande C, et al. Conditioning regimens in autologous stem cell transplantation for multiple myeloma: a comparative study of efficacy and toxicity from the Spanish Registry for Transplantation in Multiple Myeloma. *Br J Haematol*. 2000;109:138-147.
17. Barlogie BM, Shaughnessy J, Sawyer J, et al. Total Therapy II (TTII) for newly diagnosed multiple myeloma (MM): preliminary data on feasibility and efficacy in the first 231 enrolled patients; comparison with predecessor trial Total Therapy I (TTI) (N = 231) [abstract]. *Blood*. 2001;98 Suppl 1:352a.
18. Donato M, Weber D, Alexanian R, et al. High dose topotecan melphalan and cyclophosphamide (TMC): a new regimen for autologous transplantation in multiple myeloma [abstract]. *Blood*. 2000;96 Suppl 1:798a.
19. Giralt S, Champlin R, Alexanian R, et al. Results of a Phase I/II trial with ¹⁶⁶Ho-DOTMP plus high dose chemotherapy in patients with multiple myeloma [abstract]. Presented at the VIII International Multiple Myeloma Workshop, Banff, Alberta, Canada, May 4-8, 2001.