High-Dose Therapy for Refractory Multiple Myeloma: Improved Prognosis With Better Supportive Care and Double Transplants

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One hundred and thirty-five patients with advanced and refractory myeloma received one of three high-dose therapy regimens: melphalan at doses of 90 to 100 mg/m² (MEL 100; 47 patients) without autotransplant; total body irradiation (TBI; 850 cGy) with either melphalan 140 mg/m² or thiotepa 750 mg/m² and autologous bone marrow transplant (ABMT) (≤30% plasma cells; 21 patients); melphalan 200 mg/m² (MEL 200) supported by both peripheral blood stem cells (PBSC) and ABMT plus GM-CSF intended as a double-transplant program (67 patients; 42 have completed and 3 are still awaiting a second autotransplant; 5 additional patients received an allograft for their second transplant). Mortality within 2 months of therapy was 20% to 25% with MEL 100 and TBI regimens, but less than 1% with MEL 200, mainly because severe neutropenia (<500/μL) was shortened to less than 1 week due to infusion of PBSC and use of growth factor therapy. Low β2-microglobulin (β2M) levels ≤ 2.5 mg/L and MEL 200 therapy were identified as the two most important independent favorable variables associated with prolonged event-free survival (EFS) and overall survival (OS). On the basis of these two parameters, three risk groups were defined: 29 good-risk patients with low β2M receiving MEL 200 had the best outcome, with median durations of EFS of 37 months and projected OS of ≥43 months; 54 intermediate-risk patients displaying one of the two favorable parameters had EFS and OS durations of 16 and 36 months, respectively; and 52 poor-risk patients with high β2M not receiving MEL 200 had a dismal prognosis, with EFS of 3 months and OS of 5 months (all $P < .0001$). Further analysis that excluded treatment as a variable identified high β2M and resistant relapse as the two major adverse prognostic factors, one of which was present in 80% of the 135 patients. Among these 108 high-risk patients, prognosis was improved markedly with MEL 200 because of both better supportive care (PBSC and hematopoietic growth factors) and more intensive therapy using the double-transplant approach. This study supports the concept that safer and potentially more-effective therapies can be developed in the setting of advanced and resistant disease.

MULTIPLE MYELOMA (MM) remains an incurable malignancy.[1] Recent efforts have been devoted to evaluating dose intensification to the point of bone marrow (BM) ablation requiring hematopoietic stem cell support.[2,3] These approaches were initially piloted in patients with refractory myeloma[4,5] and are currently being evaluated in earlier disease stages.[6-10]

Our group had previously observed, in a trial with total body irradiation (TBI, usually 850 cGy) with either melphalan 140 mg/m² or thiotepa 750 mg/m² and autologous BM support (up to 30% plasma cells), that patients with resistant relapse had an especially dismal prognosis, whereas those with primary unresponsive disease fared as well as those with sensitive myeloma receiving such high-dose therapy for response consolidation.[4] Over the past 5 years, we have developed a double-transplant procedure using both peripheral blood stem cells (PBSC) and autologous BM transplant (ABMT) together with granulocyte-macrophage colony-stimulating factor (GM-CSF).[10] PBSC had been collected after high-dose cyclophosphamide (HDCTX) priming with GM-CSF.[11]

We now report our collective experience in 135 patients with refractory MM, receiving intravenous melphalan at 90 or 100 mg/m² without transplant (MEL 100); TBI with either melphalan 140 mg/m² or thiotepa 750 mg/m² with ABMT (TBI); and melphalan 200 mg/m² (MEL 200) supported with both PBSC and ABMT, with the intent to administer two successive transplants within 6 months. Those MEL 200 patients not achieving at least a partial remission (PR) (see below) or relapsing after one transplant with MEL 200 were offered melphalan 140 mg/m² and TBI for their second transplant or an allogeneic transplant if they had a compatible sibling donor. Prognostic factor analysis identified a low pretransplant β2-microglobulin level (β2M) level (≤2.5 mg/L) and primary unresponsive MM (rather than resistant relapse) as two independent parameters associated with superior event-free survival (EFS) and overall survival (OS). When treatment was included in the analysis as a variable, low β2M and MEL 200 emerged as the two most important favorable features, permitting identification of three risk categories. These results support the hypothesis that further intensification of therapy to the point of a double transplant effects further tumor-mass reduction, and hence, extends remission and survival times.

PATIENTS AND METHODS

The diagnosis of MM used standard criteria.[12] All patients had resistant MM as defined by disease progression (greater than 25% increase in myeloma protein concentration in serum and/or 24-hour Bence Jones proteinuria) despite adequate doses of salvage therapy usually with at least three cycles of high-dose dexamethasone (DEX) pulsing or vincristine, doxorubicin, and dexamethasone (VAD).[13,14] Primary unresponsiveness implied failure of ever having responded with ≥75% tumor cytoreduction; resistant relapse was defined as a relapse from a prior remission (≥75% regression) that failed to respond to DEX or VAD.

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Submitted January 10, 1994; accepted March 28, 1994.

Supported in part by Grant No. CA 55819 from the National Cancer Institute, and the American Cancer Society.

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0006-4971/94/8403-0012$3.00/0

Table 1. High-Dose Therapy for Refractory MM: Patient Characteristics (N = 135)

Parameter	MEL 100	TBI*	MEL 200	p1†	p2	p3	p4
Total (N)	47	21	67				
Age > 50	47%	57%	54%	.4	.8	.5	.5
>12 Mos of Prior Rx	51%	86%	52%	.007	.006	.9	.3
B2M > 2.5 mg/L pre-Tx	81%	67%	57%	.2	.4	.007	.01
LDH > 170 U/L pre-Tx	85%	76%	21%	.4	.0001	.0001	.0001
Resistant relapse	49%	67%	36%	.2	.01	.2	.03

* 850 cGy with melphalan 140 mg/m^2 or thiotepa 750 mg/m^2.

† p1, MEL 100 *v* TBI; p2, TBI *v* MEL 200; p3, MEL100 *v* MEL 200; p4, combined MEL 100/TBI *v* MEL 200.

Table 1 summarizes patient characteristics in the three different treatment groups. MEL 100 included 14 patients receiving 90 mg/m^2 and 9 patients receiving 100 mg/m^2 of intravenous melphalan between 1985 and 1990[15]; since 1989, 24 additional patients receiving melphalan 100 mg/m^2 were supported with GM-CSF at a dose of 250 μg/m^2 subcutaneously.[16] None of the MEL 100 patients received transplant support. TBI (850 cGy; with melphalan 140 mg/m^2, 18 patients; with thiotepa 750 mg/m^2, 3 patients) was evaluated between 1985 and 1990 in 21 patients with ABMT that contained $\leq$30% plasma cells.[4] On a per-kilogram body-weight basis, at least 1.0 $\times$ 10^8 mononuclear cells and 1.5 $\times$ 10^4 CFU-GM were required.

MEL 200 was administered to 67 patients between 1990 and 1993 with the intent of a double transplant within 6 months.[10] Of the 67 patients, 39 had received prior DEX or VAD and alkylating agent regimens such as melphalan-prednisone (22 patients), VMCP-VBAP (9 patients), or VBMCP (M2 protocol, 8 patients). Four had received only alkylating drugs and 24 only DEX or VAD. Among the 41 patients with primary unresponsive MM, 68% had been refractory for greater than 6 months and 37% for greater than 12 months.

With MEL 200, PBSC had been collected after administration of high-dose cyclophosphamide at 6 g/m^2 followed by daily subcutaneous administration of GM-CSF at 250 μg/m^2, as previously described[10]. In addition, 62 of the 67 patients also had autologous BM harvested, usually within 6 weeks from HDCTX administration. A first cycle of MEL 200 was administered in two doses of 100 mg/m^2 each on days -3 and -2, followed on day 0 by infusion of PBSC and BM, followed on day +1 by daily subcutaneous injection of GM-CSF 250 μg/m^2 until hematopoietic recovery (granulocytes greater than 2,000/μL on 3 successive days). Three to 6 months later, a second autotransplant was scheduled.

The decision as to proceeding with a second transplant depended on the quantity and quality of available hematopoietic stem cells and tolerance of the first transplant. Eleven patients with PBSC less than 4 $\times$ 10^8 and autologous marrow less than 2 $\times$ 10^8 were given only one autotransplant with MEL 200. The remaining 56 patients with PBSC greater than 6 $\times$ 10^8 and/or autologous BM greater than 3 $\times$ 10^8 were candidates for two autotransplants. In the absence of relapse, 24 patients achieving PR (see below) received a second cycle of MEL 200. When the first transplant with MEL 200 failed to effect at least PR or relapse ensued after PR, melphalan 140 mg/m^2 plus TBI 850 cGy (11 patients) or 1020 cGy (7 patients) was given. Currently, 3 patients are eligible for their second autotransplant, 3 declined further therapy and 3 died after the first cycle of MEL 200 (toxicity, 1 patient; recurrent MM, 2 patients). Five other patients went on to allogeneic transplant using HLA-identical sibling donors after busulfan 14 mg/kg and cyclophosphamide 120 mg/kg. Of the 67 patients receiving MEL 200, two autotransplants were actually administered to 31 patients (46%) within 6 months, and to 42 (63%) within 1 year. Considering the five additional allotransplants, altogether, 70% received 2 transplants. All patients provided written informed consent to the investigational treatment according to institutional policies.

Supportive care measures included prophylactic antibiotics with either oral ciprofloxacin or trimethoprim-sulfamethoxazole. Recombinant human erythropoietin at a dose of 10,000 U subcutaneously thrice weekly was used in over 50% of the 67 patients receiving MEL 200. Platelet transfusions were administered when platelets dropped below 20,000/μL and packed red blood cells were transfused when hemoglobin decreased to levels below 8 g/dL. Upon completion of hematopoietic recovery, 42 of 67 MEL 200 patients received posttransplant interferon α2b (IFNα2b) at an initial dose of 3 $\times$ 10^6 U/m^2 thrice weekly subcutaneously until disease progression. IFN was discontinued because of undue toxicity in about one third of patients.

Response was defined as partial when patients achieved $\geq$75% tumor-mass reduction including decrease in Bence Jones proteinuria to less than 100 mg per day and in BM plasmacytosis on aspirate and biopsy examination to less than 5%. A complete remission (CR) required the absence, in both serum and urine, of monoclonal protein on immunofixation analysis as well as a normal BM aspirate and biopsy including the absence of monoclonal plasma cells on DNA/cytoplasmic Ig flow cytometry[17]. Early death referred to any deaths within 60 days of high-dose therapy. EFS and OS are reported from initiation of high-dose therapy. An "event" was defined as disease relapse or death caused by MM or other causes.

Statistical methods included chi-square tests for comparison of rates[18]; Kaplan-Meier estimates of relapse-free and overall survival curves[19]; and log-rank test[20] for comparison of curves. Multivariate analyses were done using Cox regression models.[21] Variables examined before autotransplant included age, β2M, lactate dehydrogenase (LDH), Ig isotype, duration of prior therapy, primary resistance versus resistant relapse, as well as the type of high-dose therapy applied. A test for treatment differences, adjusting for prognostic factors, is sometimes called an analysis of covariance.[22] Results with MEL 200 were examined on an intent-to-treat basis.

RESULTS

The three treatment groups differed markedly in four prognostic parameters (Table 1). Compared with the other patients, those receiving MEL 200 had a significantly lower incidence of LDH and β2M elevation, resistant relapse and greater than 12 months of prior therapy. These data indicate accrual of more favorable patients with resistant MM in recent years. Figure 1 depicts the clinical outcome according to treatment regimen. Table 2 compares EFS and OS in primary refractory disease and resistant relapse. Noteworthy are the short median durations of EFS and OS with both MEL 100 and TBI of $\approx$6 months among patients with resistant relapse, which were extended with MEL 200 to 17 months for EFS (P = .0007) and to 21 months for OS (P =.006). Primary unresponsive MM had comparable prognosis with TBI and MEL 200: median EFS was $\approx$3 years,

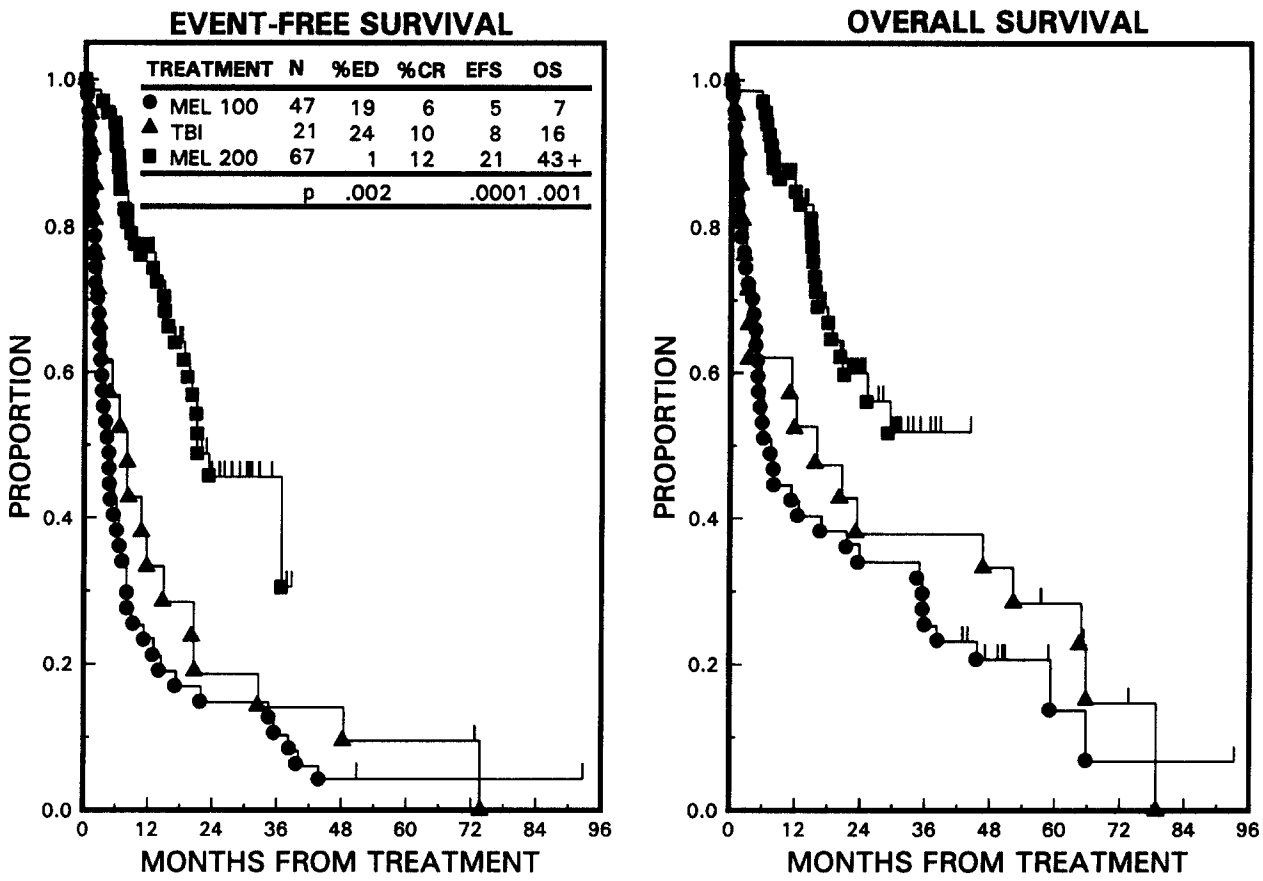

Fig 1. Clinical outcome in refractory myeloma according to treatment regimens. Superior event-free (left) and overall survival (right) after MEL 200 compared with TBI and MEL 100 regimens (for details, see text).

whereas the median survival was 66 months with TBI and has not been reached at 43 months with MEL 200. CR rates of 10% to 20% were noted with MEL 200 in both the primary unresponsive and resistant relapse groups. Early mortality (≤2 months) was only 1% with MEL 200 as opposed to 19% with MEL 100 and 24% with TBI (P = .002), mainly as a result of shortened granulocytopenia with cyclophosphamide-primed PBSC added to ABMT (Fig 2).

Several pretreatment variables affected EFS and OS (Table 3). Low β2M, primary unresponsive disease, low LDH, less than 12 months of prior therapy, and younger age (≤50 years) were all favorable features. In addition, the treatment regimen influenced prognosis markedly: MEL 200 effected median durations of EFS and OS of 21 and 43+ months, respectively, which were much longer than the 5 and 7 months with MEL 100 and the 8 and 16 months with TBI regimens. Less than 1 year of prior therapy was the only significant parameter associated with higher CR rate.

Because of the difference in several major prognostic variables among the three treatment groups (see Table 1), a multivariate regression analysis of pretreatment features was performed, which adjusts for these disparities and helps define those parameters independently affecting outcome (Table 4). Including treatment as a variable, low β2M level and

Table 2. High-Dose Therapy for Refractory Myeloma: Effect of Treatment Regimen (N = 135)

Regimen	Primary Unresponsive	Resistant Relapse	N	%ED (P)	%CR (P)	Median mos EFS (P)	Median mos OS (P)
MEL 100	+		24	21	8	4	7
		+	23	17	4	5	7
TBI	+		7	0 (.07)	29 (.04)	32 (.007)	66 (.007)
		+	14	36	0	4	7
MEL 200	+		41	2	10	37 (.006)	43+ (.01)
		+	26	0	19	17	21

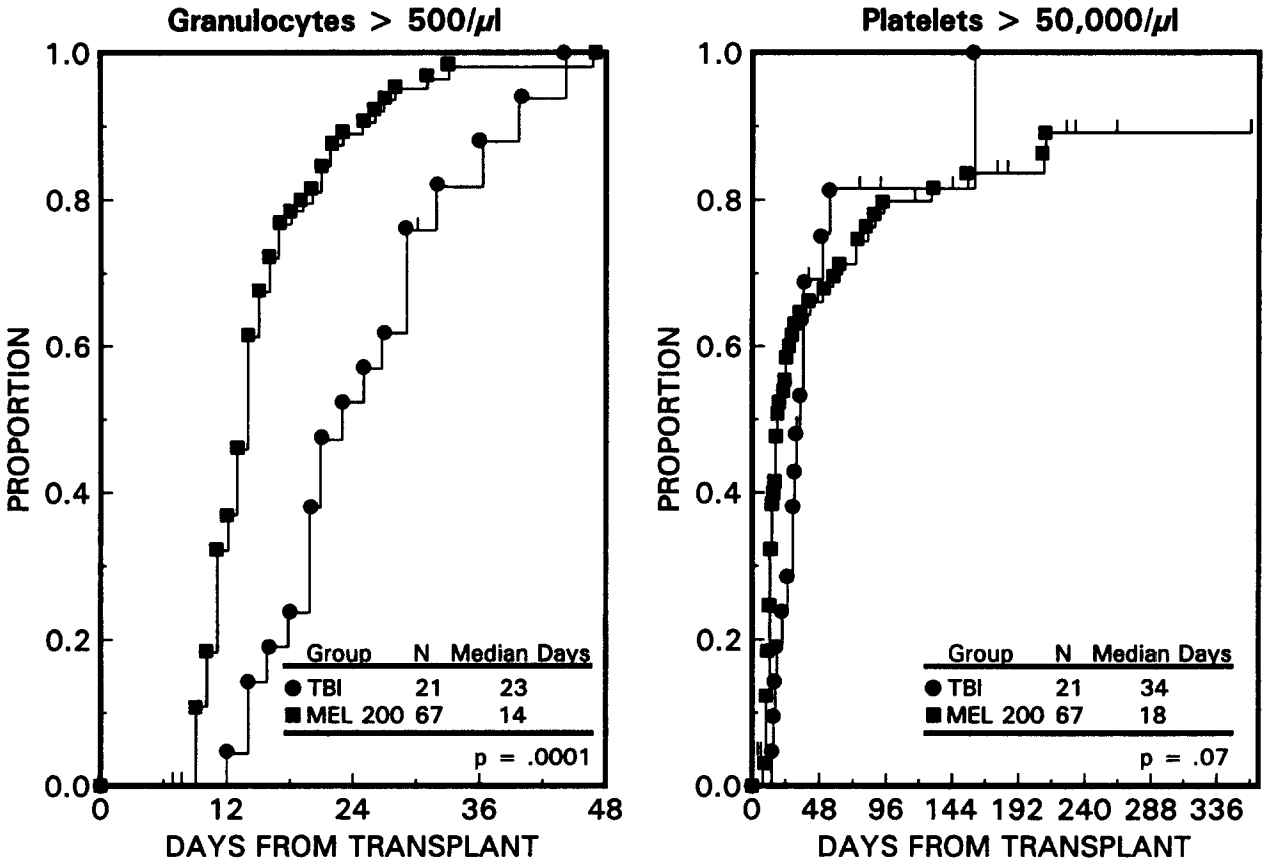

Fig 2. Hematopoietic recovery after PBSC + ABMT + GM-CSF (MEL 200) versus ABMT alone (TBI). Significantly faster granulocyte recovery with PBSC added to autologous BM in support of MEL 200 than with BM autografts alone given with TBI.

Table 3. Intensive Therapy for Refractory Myeloma (N = 135): Prognostic Factors

Parameter	N	%ED (*P*)	%≥PR	%CR (*P*)	EFS (*P*)	OS (*P*)
B2M						
≤2.5 mg/L	45	4	53	13	35	52 (.0001)
>2.5 mg/L	90	14	50	8	7 (.0001)	12
1° Unresponsive	72	8	51	11	21 (.0004)	47 (.0003)
Resistant relapse	63	14	51	8	8	15
MEL 100	47	19 (.7)	40	6	5 (.3)	7 (.4)
TBI	21	24	76	10	8	16
MEL 200	67	1 (.0004)	58	12	21 (.0007)	≥43 (.05)
Age						
≤50	65	8	49	12	16 (.03)	36 (.007)
>50	70	14	53	7	8	15
Mos from Dx						
≤12	57	5 (.06)	53	16 (.04)	20 (.07)	38 (.02)
>12	78	15	50	5	8	15
LDH						
≤170 U/L	66	8	58	11	18 (.03)	25 (.2)
>170 U/L	69	14	45	9	8	16

Abbreviations: PR, partial remission; Dx, diagnosis.

Table 4. Multivariate Analysis of Favorable Variables

Without Treatment as Variable		With Treatment as Variable	
EFS Parameter (*P*)	OS Parameter (*P*)	EFS Parameter (*P*)	OS Parameter (*P*)
B2M ≤ 2.5 mg/L (.0001)	B2M ≤ 2.5 mg/L (.0001)	B2M ≤ 2.5 mg/L (.0001)	B2M ≤ 2.5 mg/L (.0001)
Primary unresponsive (.0007)	Primary unresponsive (.006)	MEL 200 (.0001)	MEL 200 (.002)
LDH ≤ 170 U/L (.03)	≤12 mos from Dx (.1)	Primary unresponsive (.004)	≤12 mos from Dx (.008)
Age ≤ 50 (.3)	Age ≤ 50 (.2)	Age ≤ 50 (.04)	Age ≤ 50 (.05)

Abbreviations: Dx, diagnosis.

therapy with MEL 200 were the two most important favorable parameters for both EFS and OS. EFS was also superior with primary unresponsive MM and age ≤50, whereas OS was prolonged with less prior therapy and younger age.

The dominant favorable roles of both low β2M and MEL 200 recognized on multivariate analysis led us to use these two variables to define different risk groups among patients with refractory MM. The 29 patients who both exhibited low β2M and received MEL 200 had the best outcome (good risk); 54 patients with either low β2M or receiving MEL 200 constituted an intermediate risk group, whereas those 52 with high β2M and not receiving MEL 200 had a dismal prognosis (poor risk) (Table 5 and Fig 3).

A second strategy was applied to address the imbalance in prognostic factors, which were significantly more favorable in the MEL 200 group compared with MEL 100/TBI (now referred to as "no MEL 200") (see Table 1). Multivariate regression analysis without treatment as a variable showed, for both EFS and OS, low β2M and primary unresponsive MM (rather than resistant relapse) to be the two most significant variables associated with favorable outcome (Table 4). This was true for all 135 patients and the subgroups receiving MEL 200 or no MEL 200. The good-risk group of 27 patients exhibiting both favorable features had significantly lower mortality (0% *v* 14%) and longer EFS and OS than the remaining 108 subjects (37 *v* 8 months and 66 *v* 16 months, respectively) (Table 6). When treatment was examined (MEL 200 *v* no MEL 200) in the good- and poor-risk categories, MEL 200 provided superior outcome with lower early mortality and longer EFS and OS compared with no MEL 200, especially in the poor-risk category (less than 2 favorable variables), constituting 80% of all patients (Table 6).

Landmark analyses at 1 and 2 months after high-dose therapy showed that poor-risk patients receiving MEL 200 fared better than those in the no MEL 200 group (Table 7). This implies that improved outcome with MEL 200 was not simply related to better supportive care with PBSC and hematopoietic growth factors, but to greater tumor cytoreduction accomplished with two transplants.

DISCUSSION

This report represents the largest series of intensive therapy for MM administered in the setting of refractory disease, using progressively more intensive therapy and improved supportive care. The high early mortality of about 25% with TBI was virtually eliminated in the MEL 200 group, mainly as a result of rapid hematopoietic engraftment with PBSC added to ABMT with hematopoietic growth factors. In support of this conclusion was the observation of a similarly low mortality among the 42 second-transplant recipients in the MEL 200 group, whether MEL 200 was applied twice (no death among 24 patients) or TBI was added (one death among 18 patients). MEL 200 also prolonged EFS and OS markedly, especially among patients with resistant relapse. In adjusting for the heterogeneity in patient and disease characteristics present among the three treatment groups, multivariate regression analysis was applied that identified low β2M, reflecting low tumor mass, and MEL 200 (rather than TBI or MEL 100) as the two most important independent favorable features associated with prolonged EFS and OS. On the basis of these two features, three risk groups could be identified with markedly different prognoses. A superior outcome after MEL 200 was confirmed by a separate multivariate analysis that excluded treatment as a variable and identified low β2M and primary unresponsive MM as principal favorable parameters (Table 4). Among the 80% of patients in the poor-risk category (less than two favorable features; Table 6), MEL 200 was superior to the remaining therapies both with lower mortality and marked extension of EFS and OS. Longer EFS and OS in patients with primary refractory MM as opposed to resistant relapse was partly explained by fewer months of prior treatment before high-dose therapy in the former group (median of 10 months *v* 33 months with resistant relapse, $P = .0001$). However, as shown by multivariate analysis of pretreatment variables,

Table 5. Clinical Outcome According to β2M and MEL 200

					Median mos	
Risk	Parameters	N	%ED	%CR	EFS	OS
Good	B2M ≤ 2.5 and MEL 200	29	0	21	37	43+
Intermediate	B2M ≤ 2.5 or MEL 200	54	6	4	16	36
Poor	B2M > 2.5 and no MEL 200	52	23	10	3	5
P			.002	.04	.0001	.0001

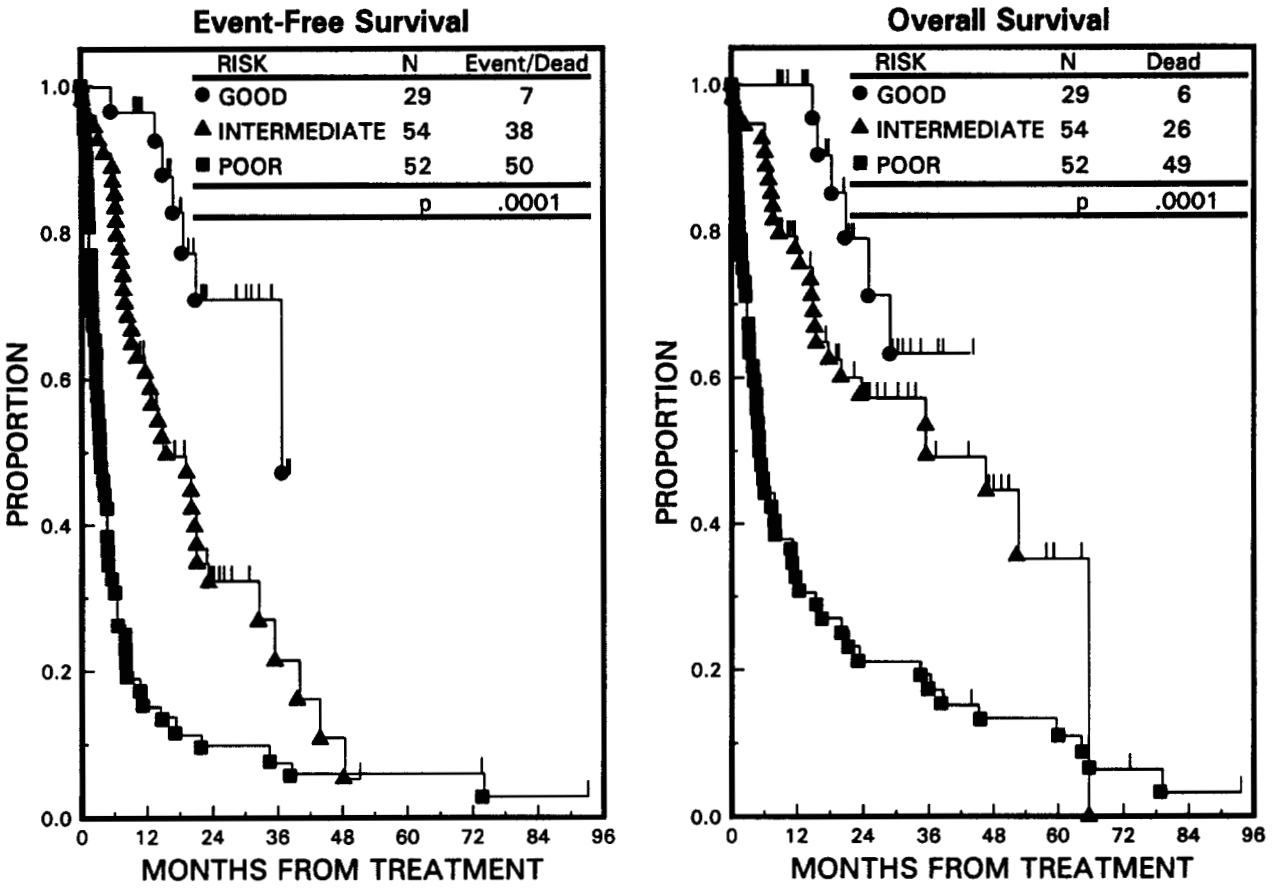

Fig 3. Event-free and overall survival differed markedly according to β2M levels before high-dose therapy and the specific regimen applied. Good-risk patients had β2M ≤ 2.5 mg/L and received MEL 200; intermediate risk was observed in the presence of one of these two favorable variables; poor risk was noted with high β2M and when other regimens were applied (MEL 100 or TBI).

the type of resistance was the principal feature, whereas differences in prior therapy duration did not retain independent significance (Table 4).

The major observation of this investigation is that further dose intensification with MEL 200 with tandem autotransplants was successfully applied to 63% of patients within 1 year and resulted in extended EFS and OS, independent of other well-recognized favorable prognostic variables, such as low β2M. These results support the concept of "more is better" for myeloma, confirming our contention that resistance of therapy can be overcome by increasing dose intensity as approached with tandem transplants. The use of cyclophosphamide-primed PBSC and hematopoietic growth factors assured rapid hematopoietic engraftment, thereby reducing the incidence of serious infections and virtually eliminating mortality. Based on the greater efficacy of tandem autotransplants in patients with refractory MM, a similar approach is currently under investigation in recently diag-

Table 6. Prognosis According to Pretreatment Variables and the Influence of Therapy

Favorable Variables*	Treatment	N	%ED (*P*)	%CR	Median mos EFS (*P*)	Median mos OS (*P*)
2	Any	27	0 (.04)	11	37 (.0002)	66 (.0001)
<2	Any	108	14	10	8	16
2	MEL 200	19	0	16	39+ (.03)	43+ (.6)
	No MEL 200	8	0	0	20	66
<2	MEL 200	48	2 (.001)	13	19 (.0001)	25 (.001)
	No MEL 200	60	23	8	4	6

* B2M ≤ 2.5 mg/L, primary unresponsive MM.

Table 7. One- and Two-Months Landmark Analysis Unfavorable Group

Landmark	Treatment	N	%ED (P)	%CR	Median mos EFS (P)	Median mos OS (P)
1 mo	MEL 200	47	0	13	19	25
	No MEL 200	53	15 (.005)	9	5 (.0001)	8 (.006)
2 mo	MEL 200	47	0	13	19	25
	No MEL 200	47	0	11	5 (.0002)	12 (.04)

B2M > 2.5 mg/L and/or resistant relapse.

nosed patients. Timely administration of two autotransplants was feasible in about 80% of these patients, resulting in CR rates exceeding 50% and 3-year projections for EFS and OS of 75% and 80%, respectively.[23]

A considerable relapse rate is still being observed after tandem autotransplants. It is unknown whether these relapses are the consequence of inadequate tumor cytoreduction or caused by tumor cells contaminating BM and PBSC transplants, or a combination of the two. Future studies will be directed toward the infusion of tumor-free transplants in combination with a more intensive preparative regimen for the second transplant that includes high-dose melphalan and TBI.

ACKNOWLEDGMENT

The authors greatly appreciate the technical assistance of Sandy Thompson-Mattox, Dwayne Bracy, and Lela Vaught, as well as the secretarial help provided by Christina Bewley and Madeline Scallan.

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