Bone Marrow Transplantation, (1998) 21, 1101–1107

http://www.stockton-press.co.uk/bmt

Long-term follow-up after high-dose therapy for high-risk multiple myeloma

B Barlogie[1], S Jagannath[1], S Naucke[1], S Mattox[1], D Bracy[1], J Crowley[2], G Tricot[1] and R Alexanian[3]

[1]*Myeloma and Transplantation Research Center and Arkansas Cancer Research Center, University of Arkansas for Medical Sciences, Little Rock, AR;* [2]*Southwest Oncology Group Statistical Center, Seattle, WA; and* [3]*UT MD Anderson Cancer Center, Houston, TX, USA*

Summary:

Between 1985 and 1990, 133 patients with advanced multiple myeloma (MM) (74% resistance; 41% resistant relapse, RR) were treated with five high-dose therapy (HDT) regimens including: melphalan ⩽100 mg/m^2 (MEL 100) (46 patients); MEL 100 plus GM-CSF (24 patients); MEL 140 plus autologous bone marrow transplantation (ABMT) (eight patients); MEL 140 plus TBI 850 cGy plus ABMT (37 patients); and thiotepa 750 mg/m^2 (THIO 750) + TBI 850 cGy plus ABMT (18 patients). The median follow-up of alive patients as of December 1997 was 9 years. Overall, 17% experienced treatment-related mortality within 60 days (TRM) and 12% achieved stringently defined complete remission (CR) with a median duration of 16 months; four of 16 patients (25%) remain in CR at 10 years. The median durations of event-free survival (EFS)/overall survival (OS) were 6/15 months. Superior EFS/OS were noted with MEL 100 plus GM-CSF and the two TBI-containing regimens (9/24 months among 79 patients) compared to the remaining 54 patients receiving MEL ⩽100 or MEL 140 plus ABMT (3/5 months) (*P* = 0.0001/0.0001, respectively). Multivariate regression analyses (MVA) were performed so that, despite patient heterogeneity among the five treatment groups, potentially relevant disease, host, treatment, and supportive care variables could be identified that were associated with TRM, CR, EFS and OS. TRM was higher with creatinine >2.0 mg/dl, absence of ABMT/GM-CSF support and age >50 years; CR was superior with TBI-containing regimens and ⩽12 months of prior therapy; EFS and OS both were longer with B2M ⩽2.5 mg/l, age ⩽50 years, absence of RR and with ABMT/GM-CSF support. In the presence of >2 favorable variables (32% of patients), median EFS/OS durations of 18/48 months were observed which progressively declined with 2 and <2 favorable parameters to 6/11 months (28% of patients) to 3/5 months (40% of patients) (*P* = 0.0001/0.0001). At 10 years, 10 and 20% of patients with >2 favorable variables were event-free and alive, which was also true for the 37 patients receiving MEL 140 plus TBI. To appreciate possible long-term contributions of supportive care or treatment intensity, landmark analyses performed at 1, 2, 4 and 6 months revealed virtually identical ranking orders of prognostically favorable variables to those seen pre-HDT; once supportive care was accounted for, regimen intensity with added TBI did not emerge as an independent favorable feature.

Keywords: myeloma; autotransplant; long-term survival

Three decades of therapeutic research have, unfortunately, not advanced the prognosis of patients with symptomatic multiple myeloma (MM).[1] This is not surprising, in retrospect, since most trials involved, by design, only mildly myelosuppressive therapy even when other cytotoxic agents were added to standard melphalan-prednisone (MP).[2] As a result, true complete responses (CR) were achieved in no more than 5% of patients and, dependent upon prognostic factors, median survival typically did not exceed 30–36 months. It was not until the pioneering work of the late Tim McElwain that the concept of dose intensity was also applied to patients with MM who had generally been considered too brittle for such an approach because of profound immunosuppression, impaired pulmonary function due to rib and vertebral compression fractures, advanced age and renal insufficiency.[3] It was the observation of true CRs in high-risk disease following a single administration of melphalan at a dose of 140 mg/m^2 (MEL 140) without hemopoietic stem cell or growth factor support that prompted our group and others to explore high-dose therapy (HDT) systematically, initially in patients with advanced and refractory disease and, subsequently, in high-risk MM upon achieving an initial remission or responding to salvage therapy.[4–15]

This report summarizes our experience with HDT in 133 MM patients, accrued between 1985 and 1990, using unsupported or hemopoietic growth factor (GM-CSF)-supported MEL up to a dose of 100 mg/m^2,[4,5] and bone marrow autograft (ABMT)-supported MEL 140,[6] MEL 140 and added total body irradiation (TBI; 850 cGy) or, when MEL was temporarily unavailable, thiotepa 750 mg/m^2 (THIO 750) + TBI.[7,8]

Correspondence: Dr B Barlogie, Myeloma and Transplantation Research Center, University of Arkansas for Medical Sciences, 4301 W Markham, Slot 508, Little Rock, AR 72205, USA
Received 8 August 1997; accepted 16 November 1997

Patients and methods

One hundred and thirty-three patients were accrued to consecutive phase II studies reported here between 1985 and 1990, and treatment was conducted initially at the University of Texas MD Anderson Cancer Center and, since September 1989, at the University of Arkansas for Medical Sciences in Little Rock (40 patients). Patients' status was updated as of 1 December 1997.

Ninety percent of patients have died, and the median follow-up of surviving patients is 9 years. All protocols had been approved by the Institutional Review Boards, and patients had to provide written informed consent in compliance with institutional and National Cancer Institute policies. The diagnosis of MM had been established using standard criteria.[16] Prior to study enrollment, pertinent diagnostic and prognostic features of MM at diagnosis, either elsewhere or at the two institutions where the research trial was to be undertaken, were reviewed and details of treatment and response recorded.

Table 1 summarizes previously recognised prognostically relevant host- and MM-related features prior to HDT for the entire cohort of 133 patients and separately for the five treatment sub-groups (see below). Significant differences were noted with regard to B2M and LDH elevations as well as the incidence of resistant relapse. The five principal treatments included MEL ⩽100 (according to age and renal function);[4] MEL 100 + GM-CSF;[5] MEL 140 + ABMT;[6] and MEL 140 or THIO 750 + TBI 850 cGy + ABMT.[8] All patients receiving myeloablative regimens with TBI were admitted to a laminar air flow unit at MD Anderson Cancer Center. Details of these treatments and supportive care have been reported previously.[4,5,8] Resistance to prior therapy implied failure to achieve ⩾50% reduction in serum M peak concentration and/or >90% decrease in Bence Jones proteinuria despite myelosuppressive doses of standard regimens and high-dose dexamethasone (⩾2 lines of treatment). Among patients with refractory MM, those failing from the outset were considered 'primary unresponsive' and those relapsing from a prior remission but not responding to salvage regimens were deemed to have 'resistant relapse'.[4,5,8]

This report provides a final analysis of outcome according to the different treatment regimens including treatment-related mortality within 60 days (TRM), incidence of stringently defined CR (negative immunofixation analysis of serum and urine and normal bone marrow aspirate and biopsy including DNA/cIg flow cytometry for at least 2 months) as well as durations of EFS, CR and OS; events included relapse or death from any cause. Potentially relevant host (age, performance status, creatinine, hemoglobin, albumin) and disease variables (Durie–Salmon stage, B2M, LDH, Ig isotype, bone marrow plasmacytosis) as well as treatment intensity (±TBI) and supportive care, ie hemopoietic growth factor support with GM-CSF or ABMT, were also examined. Both univariate and multivariate analyses were performed to identify the key variables associated with the aforementioned endpoints. Kaplan–Meier plots were used to depict EFS and OS. Comparisons between curves were performed utilizing two-sided log-rank tests.

Results

Table 2 portrays the clinical outcome for the five subgroups. Median EFS/OS durations were shorter with MEL ⩽100 and MEL 140 + ABMT (3/5 months) when compared with the remaining regimens (9/24 months; $P = 0.0001/0.0001$, respectively) (Figure 1). TRM was highest in the MEL ⩽100 trials and was significantly lower with GM-CSF added to MEL 100 or with ABMT in support of more intensive regimens (28% *vs* 10%, $P = 0.008$). CR rates (normal marrow aspirate and biopsy and absence of monoclonal protein in serum and urine on immunofixation analysis) were higher with ABMT regimens (21% *vs* 6%, $P = 0.01$). As of last follow-up, four of 10 patients continue in CR, three after MEL 140 + TBI. The median CR duration was 16 months with 25% remaining in CR at 10 years (Figure 2). When examined separately by regimens effecting a minimum CR rate of 10%, the 12 patients receiving greater dose intensity with ABMT support had a CR duration of 22 months compared with 8 months for the four remaining patients treated with MEL 100 ± GM-CSF ($P = 0.055$) (Figure 2).

To account for the heterogeneity in disease, host, treatment and supportive care variables, multivariate regression analyses were applied, that identified the key prognostic parameters associated with the aforementioned clinical endpoints (Table 3). The treatment approach was condensed

Table 1 Patient characteristics ($n = 133$)

Parameter	*Percent of patients*						*P*
	Total (n = 133)	*MEL ⩽100 (n = 46)*	*MEL-100 GM-CSF (n = 24)*	*MEL 140 (n = 8)*	*THIO TBI (n = 18)*	*MEL-140 TBI (n = 37)*	
B2M >2.5 mg/l	68	91	71	63	61	43	0.0001
Resistant	74	100	100	100	17	49	0.0001
Resistant relapse	41	37	71	75	11	32	0.0003
LDH >190 U/l	69	91	58	38	61	59	0.001
Age >50 years	59	71	46	75	78	46	0.06
Creat >2.0 mg/dl	8	13	17	0	0	3	0.1
>1 Year of Prior Rx	64	52	58	75	78	73	0.2

Table 2 Clinical outcome according to treatment

Treatment	*n*	*% TRM*	*% CR*	*Median months*				*No. patients*	
				EFS	*P*	*OS*	*P*	*Alive*	*CR*
Total	133	17	12	6		15		10	4
MEL ⩽100	46	28	7	2		5		1	0
					0.02		0.02		
MEL 100 + GM-CSF	24	17	4	6		22		1	0
					0.8		0.7		
MEL 140 + ABMT	8	13	13	4		8		1	1
					0.8		0.2		
THIO 750/TBI + ABMT	18	0	11	7		23		0	0
					0.05		0.09		
MEL 140/TBI + ABMT	37	11	27	15		24		7	3
	P	0.1	0.04	0.0001		0.0002			

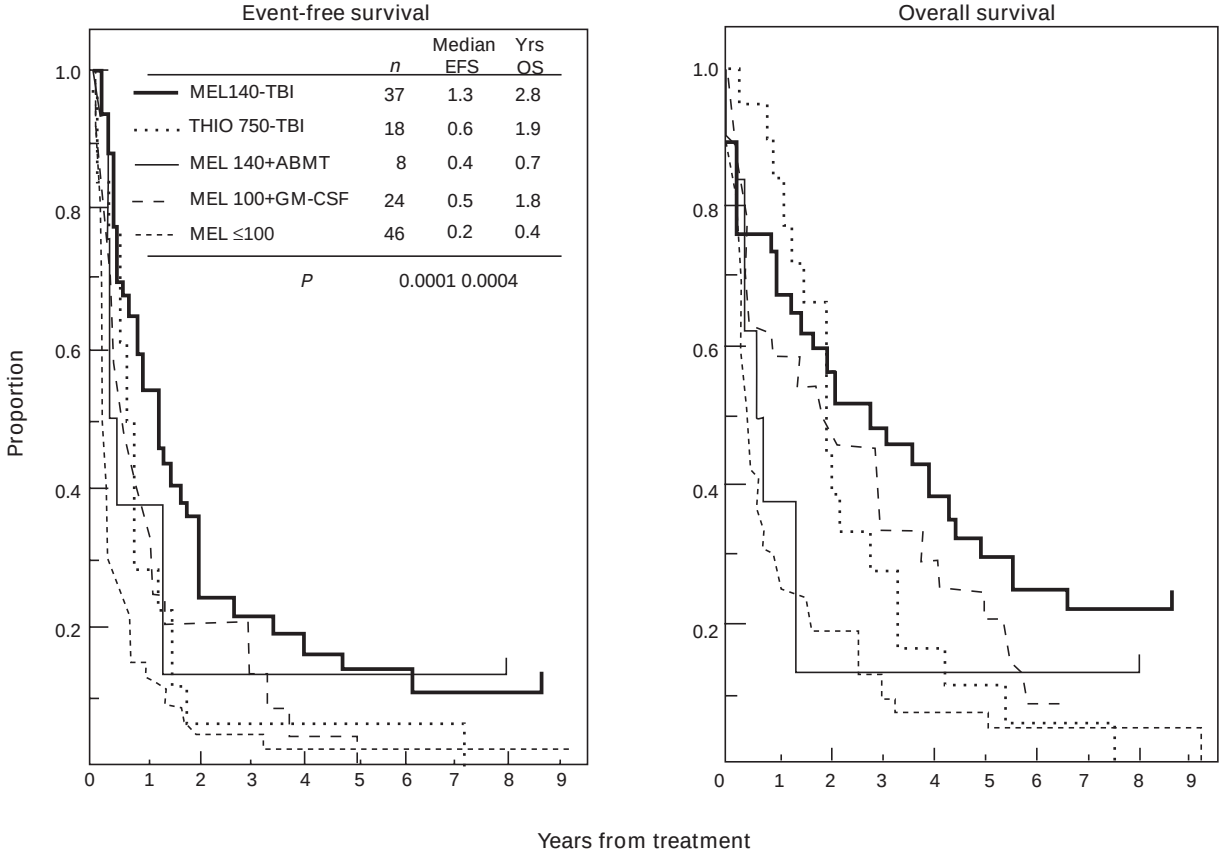

Figure 1 Event-free and overall survival from high-dose therapy of all 133 patients and separately according to different regimens employed.

to TBI-containing truly myeloablative therapy *vs* non-TBI regimens, and the importance of supportive care was examined according to whether ABMT or GM-CSF were administered. TRM was significantly higher in patients with renal impairment, in those not receiving growth factor or ABMT support and when age exceeded 50 years. Thus, the 36 patients (27%) presenting with all three favorable parameters had a TRM of only 3%, which was significantly lower than the 15% in the presence of 1 (61 patients, 46%) and the 33% when ⩾2 variables were unfavorable (36 patients, 27%) ($P = 0.002$). CR was highest with TBI-containing regimens and when prior treatment did not exceed 1 year (27 *vs* 5%, $P = 0.0002$). Both EFS and OS (following HDT) were longer in the absence of resistant relapse, with low B2M, growth factor/ABMT support and age ⩽50 years. Thus, superior outcome was observed in the presence of favorable variables with a progressive decline in both EFS and OS durations as the number of favorable parameters decreased (Figure 3): 32% of patients in the low-risk group enjoyed EFS/OS durations of 18/48 months

Table 3 Multivariate regression analysis

TRM	*P*	*CR*	*P*
Creatinine >2.0 mg/dl	0.007	TBI	0.006
No ABMT/GMCSF support	0.03	<1 year of prior therapy	0.008
Age >50 years	0.05		
EFS	*P*	*OS*	*P*
ABMT/GMCSF support	0.0001	B2M ⩽2.5 mg/l	0.0001
Non-resistant relapse	0.0001	Age ⩽50 years	0.0001
Age ⩽50 years	0.001	Non-resistant relapse	0.006
B2M ⩽2.5 mg/l	0.01	ABMT/GMCSF support	0.01

Table 4 Multivariate regression analysis

EFS	*P*	*OS*	*P*
1 Month landmark (n = 124)			
ABMT/GM-CSF support	0.0001	B2M ⩽2.5 mg/l	0.0001
Non-resistant relapse	0.0001	Age ⩽50 years	0.0001
Age ⩽50 years	0.0003	Non-resistant relapse	0.004
B2M ⩽2.5 mg/l	0.02	ABMT/GM-CSF support	0.008
2 Month landmark (n = 111)			
Non-resistant relapse	0.0001	B2M ⩽2.5 mg/l	0.0001
ABMT/GM-CSF support	0.0001	Age ⩽50 years	0.0001
Age ⩽50 years	0.003	Non-resistant relapse	0.004
B2M ⩽2.5 mg/l	0.03	ABMT/GM-CSF support	0.03
4 Month landmark (n = 97)			
Non-resistant relapse	0.0001	B2M ⩽2.5 mg/l	0.0001
ABMT/GM-CSF support	0.0001	Age ⩽50 years	0.0001
Age ⩽2.5 years	0.004	Non-resistant relapse	0.006
B2M ⩽50 mg/l	0.02	ABMT/GM-CSF support	0.1
6 Month landmark (n = 85)			
Non-resistant relapse	0.002	B2M ⩽2.5 mg/l	0.0001
B2M ⩽2.5 mg/l	0.02	Age ⩽50 years	0.0005
Age ⩽50 years	0.04	Non-resistant relapse	0.03
ABMT/GM-CSF support	0.1	ABMT/GM-CSF support	0.6

compared to 6/11 months among the 28% in the intermediate and 3/5 months in the high-risk group (40%).

In order to better appreciate possible long-term contributions of supportive care or treatment intensity, several landmark analyses were performed at 1, 2, 4 and 6 months when 124, 111, 97 and 85 patients, respectively, were alive (Table 4). The ranking order of independently significant parameters for both EFS and OS at these landmarks was virtually identical to that observed prior to HDT (see Table 3). Surprisingly, once supportive care (ABMT/GM-CSF) was accounted for, addition of TBI, and hence overall regimen intensity, did not emerge as an independent favorable feature.

Discussion

This report represents a detailed account of the long-term results (minimum follow-up, 7 years; 92% of patients have died) of early HDT pilot trials for advanced and mainly refractory MM. Although performed initially as phase II feasibility trials to determine toxicity and efficacy of what appeared to be a radical departure not only from past therapeutic approaches to patients with MM but also from the common view that autotransplants should be performed with curative intent. Ten-year EFS and OS of 11% and 19% among the 37 patients treated with MEL 140 + TBI 850 cGy was remarkable and prompted scrutiny of companion pilot studies conducted in the mid-1980s. It was surprising indeed to note long-term survivors, some of whom are disease-free, among all MEL-containing trials (see Table 2 and Figure 1). Although 10 and 15 year survivorship had been reported with standard therapy in previously untreated patients,[17,18] this report dates outcome strictly from the initiation of HDT mainly for relapsed and refractory MM. When backdated to the time of initial therapy, the median OS duration was 5 years, and 30% of those receiving MEL 140 + TBI are alive at 10 years (Figure 4). In contrast to patients' characteristics typically associated with 10 year survivorship following standard therapy, such as low tumor

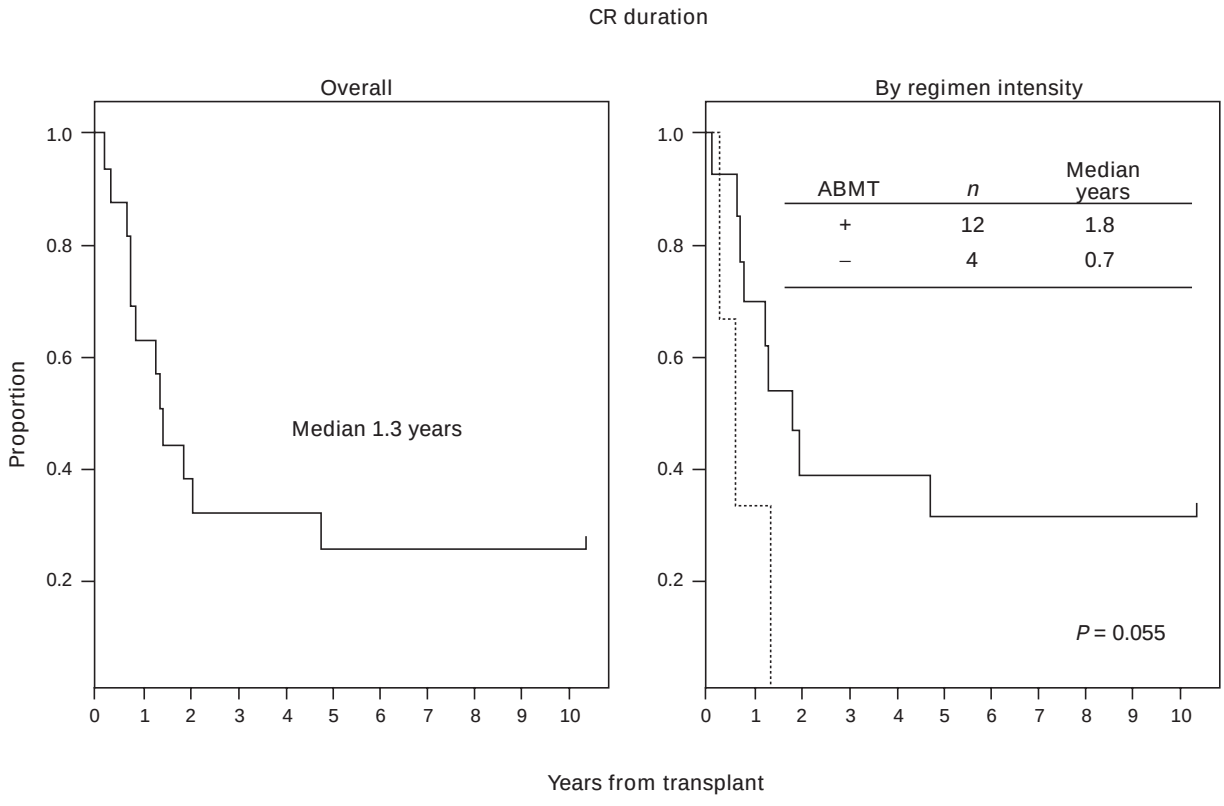

Figure 2 Duration of complete remission dated from high-dose therapy. Left panel: all 16 patients achieving CR; right panel: superior outcome with greater dose intensity requiring ABMT (median of 22 *vs* 8 months, $P = 0.055$).

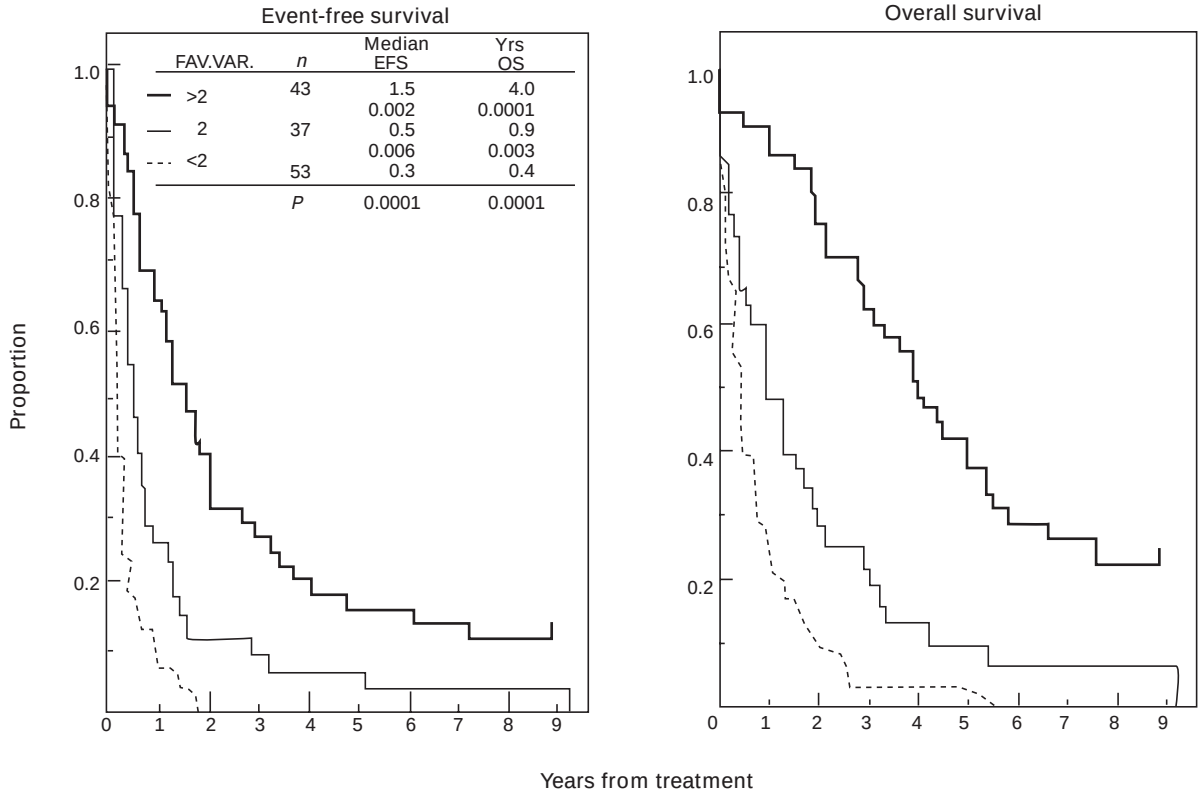

Figure 3 Event-free and overall survival from high-dose therapy according to risk factors identified on multivariate analysis (see Table 3). Distinctly different outcomes were observed as the number of favorable variables (FAV. VAR.) decreased from >2 to 2 to <2.

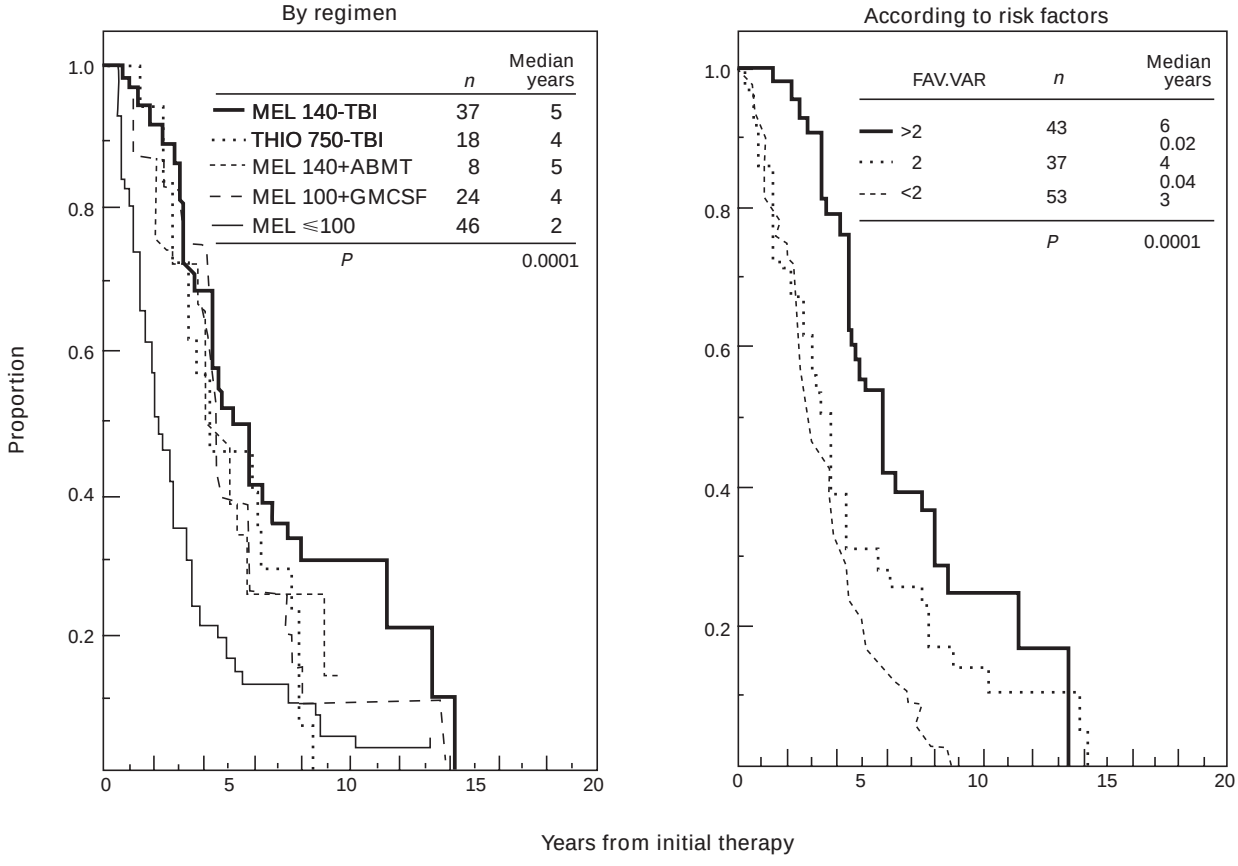

Figure 4 Survival from initial standard therapy according to different regimens employed and according to the number of favorable variables (FAV. VAR.) present prior to high-dose therapy.

mass presentation and marked response to standard therapy,[10,11] patients in this study had advanced stage III disease at diagnosis in 32% and refractory disease in 74%.

TRM was highest (28%) among patients receiving unsupported MEL ⩽100 (no GM-CSF or ABMT) and dropped significantly to 13% once supportive care with either GM-CSF for MEL 100 or ABMT for eventually myeloablative therapy with TBI was introduced ($P = 0.03$) (Table 2). As was evident from multivariate analysis, however, renal function impairment and older age increased TRM, independent of supportive care strategies (Table 3). EFS and OS were longest among patients presenting with low B2M (reflecting reduced tumor burden and/or preserved renal function), younger age, absence of resistant relapse (probably associated with hyperproliferative disease compared to primary unresponsive MM) and when better supportive care was employed (GM-CSF/ABMT) (Figure 3).

Landmark analyses revealed that regimen intensity was not an independent variable once supportive care was accounted for (Tables 3 and 4): indeed, the lower TRM with ABMT/GM-CSF (10% *vs* 28%, $P = 0.008$) contributed markedly to longer EFS (9 *vs* 2 months, $P = 0.0001$) and OS (23 *vs* 5 months, $P = 0.0001$). At 6 months after HDT, when all transplant-related fatal complications and early relapses had already occurred, the supportive care parameter lost its significance for both EFS and OS, which were now mainly affected by disease features (B2M, resistant relapse) and age. The consistent impact of supportive care on *both* EFS and OS up to 4 months after HDT attests to the toxicity of HDT for elderly MM patients when applied without cellular or growth factor support. Absence of TBI as a critical feature for long-term survival, even when analyzed at the 12 month landmark (data not shown), suggests that the increase in regimen intensity (from MEL 100 to MEL 140 + TBI) was insufficient to outweigh the importance of disease and host features in refractory and relapsed MM.

Still greater regimen intensity was explored in the late 1980s in refractory MM using two cycles of HDT, both supported by mobilized peripheral blood stem cells (PBSC), which markedly hastened neutrophil recovery to 500/μl from a median of 23 days with ABMT to just 14 days and thus decreased TRM to 5%.[19] A previously published comparison of such 'tandem autotransplants' with MEL 200, TBI-containing single ABMT and MEL 100 regimens, indicated that the greater dose intensity delivered safely with two PBSC transplants emerged as the dominant favorable prognostic feature for both EFS and OS together with pre-HDT B2M.[20] Examination of prognostic variables that included timeliness of a second HDT cycle and CR after HDT among almost 500 patients receiving tandem transplants in different disease stages confirmed the importance of these two variables in addition to cytogenetics, B2M, C-reactive protein and duration of prior therapy, whereas age did not affect outcome.[21]

Collectively, these data attest to the importance of optimal supportive care with HDT that minimizes the duration of neutropenia (mobilized PBSC); once that is assured, further dose escalation (probably better achieved with tandem autotransplants than by further intensification of a single preparative regimen) is feasible and safe, resulting in further prolongation of EFS and OS. After having demonstrated the superiority of HDT over standard therapy,[22,23] the Intergroupe Francaise du Myelome is currently testing the validity of our Phase II data in a randomized trial of one *vs* two cycles of HDT.

The observation of sustained CR in 25% of patients at 10 years following a single administration of HDT (MEL 140 + TBI, three patients; MEL 140 + ABMT, one patient) (see Figure 2) justifies optimism that timely administration of tandem transplants early during the disease course will result in durable complete responses and hence effect cure in a more sizable fraction of patients.[23,24]

Acknowledgements

The authors greatly acknowledge referring physicians for having entrusted us with their patients' management. We are indebted to Connie Marendt for excellent secretarial skills. This work was supported in part by CA55819 from the National Cancer Institute, Bethesda, Maryland.

References

1 Barlogie B, Jagannath S, Tricot G. Advances in treatment of multiple myeloma. In: Schrier R (ed). *Advances in Treatment of Multiple Myeloma*. Mosby-Year Book Inc: Illinois, 1996, pp 444–448.
2 Boccadoro M, Marmont F, Tribalto M *et al*. VMCP/VBAP alternating combination chemotherapy is not superior to melphalan and prednisone even in high-risk patients. *J Clin Oncol* 1991; **9**: 444–448.
3 McElwain TJ, Powles R. High-dose intravenous melphalan for plasma-cell leukemia and myeloma. *Lancet* 1983; **2**: 822–824.
4 Barlogie B, Alexanian R, Smallwood L *et al*. Prognostic factors with high-dose melphalan for refractory multiple myeloma. *Blood* 1988; **72**: 2015–2019.
5 Barlogie B, Jagannath S, Dixon D *et al*. High-dose melphalan and GM-CSF for refractory multiple myeloma. *Blood* 1990; **76**: 677–680.
6 Barlogie B, Hall R, Zander A *et al*. High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. *Blood* 1986; **67**: 1298–1301.
7 Barlogie B, Alexanian R, Dicke K *et al*. High dose chemoradiotherapy and autologous bone marrow transplantation for resistant multiple myeloma. *Blood* 1987; **70**: 869–872.
8 Jagannath S, Barlogie B, Dicke K *et al*. Autologous bone marrow transplantation in multiple myeloma: identification of prognostic factors. *Blood* 1990; **76**: 1860–1866.
9 Cunningham D, Paz-Ares ME, Gore ME *et al*. High-dose melphalan for multiple myeloma: long-term follow-up data. *J Clin Oncol* 1994; **12**: 764–768.
10 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.
11 Anderson KC, Andersen J, Soiffer R *et al*. Monoclonal antibody-purged bone marrow transplantation therapy for multiple myeloma. *Blood* 1993; **82**: 2568–2576.
12 Bensinger WI, Rowley SD, Demirer T *et al*. High-dose therapy followed by autologous hematopoietic stem-cell infusion for patients with multiple myeloma. *J Clin Oncol* 1996; **14**: 1447–1456.
13 Bjorkstrand B, Ljungman P, Bird JM *et al*. Autologous stem cell transplantation in multiple myeloma: results of the European group for bone marrow transplantation. *Stem Cells* 1995; **13** (Suppl. 2): 140–146.
14 Harousseau J, Attal M, Divine M *et al*. Autologous stem cell transplantation after first remission induction treatment in multiple myeloma: a report of the French registry on autologous transplantation in multiple myeloma. *Blood* 1995; **85**: 3077–3085.
15 Lokhorst HM, Meuwissen O, Verdonck L, Dekker AW. High-risk multiple myeloma treated with high-dose melphalan. *J Clin Oncol* 1992; **10**: 47–51.
16 Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. *Cancer* 1975; **36**: 842–854.
17 Kyle RA. Long-term survival in multiple myeloma. *New Engl J Med* 1983; **308**: 314–316.
18 Alexanian R. Ten year survival in multiple myeloma. *Arch Intern Med* 1985; **145**: 2073–2074.
19 Jagannath S, Vesole DH, Glenn L *et al*. Low risk intensive therapy for multiple myeloma with combined autologous bone marrow and blood stem cell support. *Blood* 1992; **80**: 1666–1672.
20 Vesole DH, Barlogie B, Jagannath S *et al*. High-dose therapy for refractory multiple myeloma: improved prognosis with better supportive care and double transplants. *Blood* 1994; **84**: 950–956.
21 Vesole DH, Tricot G, Jagannath S *et al*. Autotransplants in multiple myeloma: what have we learned? *Blood* 1996; **88**: 838–847.
22 Attal M, Harousseau JL, Stoppa AM *et al*. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *New Engl J Med* 1996; **335**: 91–97.
23 Barlogie B, Jagannath S, Vesole DH *et al*. Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. *Blood* 1997; **89**: 789–793.
24 Jagannath S, Tricot G, Vesole D *et al*. Total therapy (TT) with tandem autotransplants (2 TX) for 231 newly diagnosed patients (PTS) with multiple myeloma (MM). *Blood* 1996; **88**: 10 (Abstr. 685a).