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Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years

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Summary. The feasibility and efficacy of autologous stem cell transplantation (auto-SCT) in patients aged ≥ 70 years was analysed. Newly diagnosed ($n = 34$) and refractory multiple myeloma ($n = 36$) patients were studied. The median age was 72 years (range: 70–82·6). CD34$^+$ cells were mobilized with chemotherapy and granulocyte colony-stimulating factor (G-CSF) ($n = 35$) or G-CSF alone ($n = 35$), yielding medians of $11{\cdot}8 \times 10^6$ versus 8×10^6cells/kg respectively ($P = 0{\cdot}007$). Because of excessive mortality (16%) in the first 25 patients who received melphalan 200 mg/m^2 (MEL-200), the dose was subsequently decreased to 140 mg/m^2 (MEL-140). Median times to absolute neutrophil count (ANC) $> 0{\cdot}5 \times 10^9$/l and to platelets $> 20 \times 10^9$/l were 11 and 13 d respectively. Thirty-one patients (44%) received tandem auto-SCT. Complete remission (CR) was 20% after the first SCT and 27% after tandem SCT. Median CR duration was 1·5 years and was significantly longer for patients with ≤ 12 months of prior chemotherapy (2·6 versus 1·0 years, $P = 0{\cdot}0008$). The 3-year event-free survival (EFS) and overall survival (OS) (+ standard error, SE) were projected at 20% + 9% and 31% + 10% respectively. Tandem SCTs positively affected EFS (4·0 versus 0·7 years; $P = 0{\cdot}003$) and OS (4·0 versus 1·4 years; $P = 0{\cdot}02$) compared with single auto-SCT. In conclusion, MEL-140 is less toxic and appears equally as efficacious as MEL-200 in elderly patients. The benefits of tandem SCT in this patient population need further evaluation in a randomized trial.

Keywords: elderly, multiple myeloma, autologous transplantation, stem cell collection, tandem stem cell transplants.

Multiple myeloma (MM) is a disease of the elderly with a median age at presentation of 65–70 years (Greenlee *et al*, 2000). Advanced age has been a poor prognostic factor in several conventional chemotherapy (CT) trials with a median survival of less than 3 years, even after adjusting for the major prognostic factors (Cohen & Bartolucci, 1985; Blade *et al*, 1996; Clavio *et al*, 1996; Riccardi *et al*, 1998). This adverse effect of age has been attributed to the decreased dose intensity of therapy rather than to differences in biological characteristics of the disease (Balducci *et al*, 1988; Pileri *et al*, 1993; Corso *et al*, 1998; Quaglino *et al*, 1998). In recent reports, the presenting biological and clinical features in elderly MM patients were identical to those of younger patients (Gautier & Cohen, 1994; Kurabayashi *et al*, 1998; Rodon *et al*, 2001).

Several trials have shown that autologous stem cell transplantation (auto-SCT) is superior to CT in terms of complete remission rate (CR), event-free survival (EFS) and overall survival (OS) (Attal *et al*, 1996; Barlogie *et al*, 1999; Lenhoff *et al*, 2000). Concerns about excessive toxicity and mortality with auto-SCT led most centres to limit the enrolment age for auto-SCT to 60–65-years, thus excluding more than 50% of the patients who may benefit from the procedure (Lahuerta *et al*, 2000; Manoharan, 2000). In a previous report, we have shown that age was not an adverse parameter for patients with MM receiving auto-SCT and, hence, by itself should not constitute an exclusion criterion for auto-SCT (Siegel *et al*, 1999).

In the present analysis, we evaluated the feasibility and safety of two different doses of MEL (200 and 140) and their impact on the clinical outcome in MM patients over the age of 70 years.

PATIENTS AND METHODS

Between October 1992 and October 1999, 159 patients > 70 years were referred to the Myeloma and Transplantation Research Center at the University of Arkansas for Medical Sciences. Ninety-four patients (59%) underwent

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stem cell collection. Of the 94 patients, 70 had adequate stem cell collection and met all the eligibility criteria of the auto-SCT protocol. The remaining 65 patients (40%) were not eligible because of severe co-morbidity, lack of insurance cover, inadequate support or patient preference. We report the outcome of the 70 patients who received auto-SCT.

Inclusion criteria included acceptable cardiac (ejection fraction > 50%), pulmonary [diffusion capacity for carbon monoxide (DLCO) > 60%], and hepatic (bilirubin and transaminases < 2× upper limit) functions. They all had adequate numbers of stem cells to support at least one transplant. Poor performance status secondary to MM was not an exclusion criterion. Patients were excluded if a positive human immunodeficiency virus (HIV) was detected. All patients gave written informed consent discussing the potential benefits and risks associated with stem cell collection and auto-SCT. The protocol and consent forms had been reviewed and approved by the Institutional Review Board.

Treatment. Figure 1 illustrates the patients' flow. For first auto-SCT, 25 patients received MEL-200 mg/m^2; once excessive treatment-related mortality (TRM) was noted (16%), the dose of MEL was decreased to 140 mg/m^2 (MEL-140) in the subsequent 45 patients. The second auto-SCT was scheduled within 3–6 months. According to patient tolerance and response to the first treatment, the dose of MEL ranged from 140 ($n = 13$) to 200 ($n = 14$); four patients received other preparative regimens.

MEL was infused over 20 min. Unmanipulated grafts were infused 24 h later. Granulocyte colony-stimulating factor (G-CSF), 5 μg/kg/d, was given from d +1 until the neutrophil count was $> 0{\cdot}5 \times 10^9$/l for two consecutive days. Blood cell count, electrolytes and renal function were monitored daily. Oral levofloxacin, diflucan and acyclovir were prescribed as antimicrobial prophylaxis. Patients who developed neutropenic fever greater than 38°C received intravenous broad-spectrum coverage. Blood product support was administered to those with a haemoglobin concentration less than 8 g/dl or a platelet count $< 20 \times 10^9$/l.

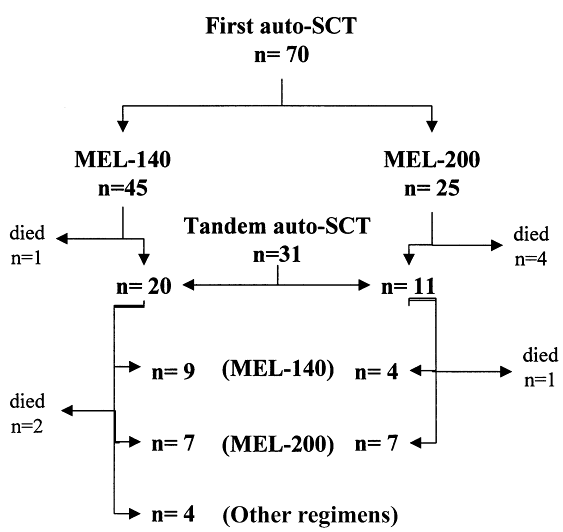

Fig 1. Flow chart depicting patient treatment.

Peripheral blood stem cells (PBSCs) were collected following high-dose cyclophosphamide (CY) 2–4 g/m^2 intravenously with subsequent G-CSF at 10 μg/kg/d from d 3 to the last day of leukapheresis. Apheresis was initiated upon recovery of leucocytes to $2{-}10^9$/l. Heavily pretreated patients and those in remission at mobilization received G-CSF alone at 10 mg/kg/d for 3 d before initiating leukapheresis.

Statistical methods. All statistical analyses were conducted using the SAS version 8 software package. For baseline comparisons, the 70 patients were divided into two groups defined by the regimen given prior to the first auto-SCT: MEL-140 versus MEL-200. Demographics and baseline features were assessed for statistically significant differences using the chi-square test, Fisher's exact test or the Kruskal–Wallis test, as appropriate. The primary endpoints analysed were incidence of CR, EFS and OS, and treatment-related mortality (TRM). We examined the impact of MEL dose and auto-SCT-2 on outcome. In order to avoid bias in favour of patients receiving second auto-SCT (auto-SCT-2), a 6-month landmark analysis was used to compare the CR rate and duration, EFS and OS. This time interval allowed 75% of the patients to receive the second SCT. Secondary endpoints analysed included the effect of the mobilization regimen on $CD\text{-}34^+$ cell yield. Kaplan–Meier methods were used to assess EFS and OS. Logistic regression modelling was used to analyse the impact of clinical variables on TRM and CR rate, while Cox regression modelling was applied to analyse their impact on the CR duration, EFS and OS. Significant univariate variables were entered along with age and first auto-SCT regimen into a multivariate final model.

Response criteria. CR required the disappearance of monoclonal gammopathy in serum and urine on immunofixation with normal bone marrow evaluation. Partial remission (PR) was defined as 75% tumour mass reduction. TRM was defined as death for any reason within 60 d following auto-SCT. Relapse was defined as recurrence of monoclonal protein or bone marrow plasmacytosis if relapse was from CR, or a 25% increase from minimal tumour mass (on two consecutive occasions) if relapse was from PR. CR duration was defined as the time from first CR to relapse or death. EFS and OS were defined as the time from first auto-SCT to progression or death. CR and EFS duration were censored at the time of last contact if patients did not experience a progression or relapse before that time. OS duration was censored at last contact if patients were still alive.

RESULTS

Patients

Table I summarizes the characteristics of the 70 patients at first auto-SCT. The median age was 72 years (range: 70–82·6). Twenty-five patients received MEL-200 and 45 received MEL-140. There was no statistical difference in baseline characteristics between the two groups except for Durie–Salmon clinical stage: 74% of the patients with stage

Table I. Baseline characteristics of MM patients > 70 at first auto-SCT.

Parameter	All ($n = 70$) %	MEL-140 ($n = 45$) %	MEL-200 ($n = 25$) %	P*
Male	73	76	68	0·5
Clinical stage III	65	74	48	0·04
IgA isotype	24	21	28	0·5
Albumin < 35 g/l	47	44	52	0·5
Creatinine > 176·8 mg/l	11	7	20	0·1
Haemoglobin < 10 mg/dl	30	33	23	0·4
B2M > 2·5 mg/l	61	62	60	0·9
LDH > 190 U/l	31	38	20	0·1
Chromosome 13 Δ†	23	20	28	0·4
> 12 months of CT	51	58	40	0·2
Status at first auto-SCT				
CR	6	2	8	0·2
Resistant disease	51	55	44	0·4
First SCT mortality	7	2	16	0·05
Second SCT given	44	44	44	0·9

*Chi-square test for independence or Fisher's test where appropriate.
†Chromosome 13 abnormalities.
Auto-SCT, autologous stem cell transplantation; B2M, beta-2 microglobulin; CR, complete remission; CT, chemotherapy; LDH, lactate dehydrogenase.

III disease in the MEL-200 group versus 48% in the MEL-140 group ($P = 0{\cdot}04$). Overall, 50% had resistant disease and 23% had partial or complete deletion of chromosome 13. Eleven per cent had a creatinine level > 176·8 μmol/l; none required haemodialysis.

A second auto-SCT was administered to 31 patients; depending on the patient's tolerance to the first auto-SCT, the regimen was MEL-200 ($n = 14$), MEL-140 ($n = 13$) or 'another regimen' ($n = 4$). Twenty out of 45 (44%) patients in the MEL-140 group and 11 out of 25 (44%) patients in the MEL-200 completed tandem SCTs ($P = 0{\cdot}9$). The median time between first and second auto-SCT was 4·5 months (range: 3·5–24) for MEL-140 group and 4·3 months (range: 3·7–40) for the MEL-200 group ($P = 0{\cdot}9$). Twenty-three out of 31 patients received a second auto-SCT within 3–6 months after the first.

Stem cell mobilization and engraftment

Thirty-five patients were mobilized with G-CSF alone and 35 received CY and G-CSF. After 3–4 d of leukapheresis, an adequate number of CD-34$^+$ cells was available for all patients to support a least one course of auto-SCT. Stem cell yield was significantly affected by mobilization regimen and duration of prior therapy (Table II). The median number of CD-34$^+$ cells after CT and G-CSF was 11·8 (range: 1·26–61·7) versus 8·06 (range: 1·13–23) × 10^6/kg after G-CSF alone ($P = 0{\cdot}007$). Patients who received 12 months or less of CT had a significantly higher CD-34$^+$ cell yield than those receiving more than 12 months (median 11·71 versus 7·18 × 10^6/kg) ($P = 0{\cdot}01$).

The median time to platelet recovery > 20 × 10^9/l was 13 d (range: 0–85) after the first and 11·5 d (range: 8–34) after the second auto-SCT. Neutrophil engraftment > 0·5 × 10^9/l was achieved at a median of 11 d (range: 8–36) following the first and 10·5 d (range: 8–16) following the second auto-SCT. The intensity of MEL in either SCT did not affect rapidity of engraftment. The percentage of patients requiring red blood cell transfusion was 54% after the first and 26% after the second SCT.

Clinical response

The median follow up was 12 months (range: 1·5–60 months); 3-year EFS and OS (± SE) were projected at 20 ± 9% and 31 ± 10% respectively (Table III). For the whole group of previously treated and newly diagnosed patients, the median OS was 24 months, EFS was 15 months and CR duration was 18 months (Fig 2).

Table II. Total CD34 × 10^6/kg cells collected, analysed by mobilization regimen and months of prior therapy.

	n*	CD 34 × 10^6/kg collected Median (range)	P†
Entire population	70	9·5 (1·1–62)	
Mobilization regimen			
G-CSF	35	8 (1·1–23)	
CY‡ & G-CSF	35	11·8 (1·3–62)	0·007
Duration of prior therapy			
< 12 months	34	11·7 (1·5–62)	
> 12 months	36	7·2 (1·1–49)	0·018

*Number of patients.
†Kruskal–Wallis Test.
‡Cyclophosphamide.

Table III. Survival of patients receiving single versus tandem auto-SCT.

		Event-free survival		Overall survival	
	Number of patients	3-years % (SE)	Median Months (range)	3-years % (SE)*	Median Months (range)
Overall	70	20 ± 9	15 (10–24)	31 ± 10	14 (16–33)
First auto-SCT	39	7·4 ± 5	9 (5–15)	15·3 ± 8·2	13 (8–23)
Tandem SCT	31	35 ± 14	29 (15–54)	46·8 ± 14	33 (24–55)

SE, standard of error; auto-SCT, autologous stem cell transplantation.

The intensity of the conditioning regimen at first auto-SCT did not affect the ultimate CR rate (28% following MEL-200 and 27% following MEL-140). Similarly, the CR rate was not significantly affected by single versus tandem SCTs: 20% versus 27% respectively. However, the CR duration was significantly longer in patients receiving MEL-200 (median 31·3 versus 15·3 months after MEL-140) ($P = 0{\cdot}04$). Using a 6-month landmark analysis, the duration of both EFS and OS was 48 months for patients receiving tandem SCTs versus 9 and 17 months, respectively, for patients receiving a single auto-SCT ($P = 0{\cdot}003/0{\cdot}02$) (Fig 3). Similarly, CR duration was longer after tandem versus single SCT (27 versus 8 months; $P = 0{\cdot}009$).

Patients were less likely to receive tandem auto-SCT if they had elevated levels of beta-2 microglobulin (B2M) or interleukin 6 (IL-6), or had refractory or resistant relapse at first auto-SCT.

The duration of prior CT significantly affected EFS and OS, irrespective of MEL-dose or the administration of tandem SCT. Median EFS/OS were 33/54 months for patients who received ≤ 12months of prior CT versus 8/16 months for patients who received > 12 months of prior CT (Fig 4). Median CR duration was also longer (2·6 years compared with 1 year) for patients who received ≤ 12 months of prior CT ($P = 0{\cdot}0008$).

Treatment-related toxicity

The median hospital stay was 16 d (range: 12–53) and was not affected by the intensity of the preparative regimen or duration of prior CT. All patients had grade III–IV neutropenia and thrombocytopenia. Fever occurred in 90% of the patients and documented bacterial infections developed in 45 patients. Severe toxicities (> grade II) associated with the first auto-SCT are presented in Table IV. Mucositis was the most frequent side-effect with grade II and higher mucositis affecting 12 out of 30 (40%) of the patients in the MEL-140 group versus 14 out of 20 (70%) in the MEL-200 ($P = 0{\cdot}03$). Pulmonary complications requiring oxygen administration were seen in 3 out 20 patients (15%) in the MEL-200 group versus none in the MEL-140 ($P = 0{\cdot}05$). Cardiac toxicity developed in 4 out of 20 (20%) in MEL-200 and in 1 out of 30 (3%) in the MEL-140 ($P = 0{\cdot}14$). However, none of the patients had a significant decrease in cardiac function following therapy. The incidence of severe diarrhoea (> grade II) was 50% (10/20) in the MEL-200 and 30% (9/30) in the MEL-140 group ($P = 0{\cdot}15$).

Early TRM with the first auto-SCT was 16% (4/25) in the MEL-200 group versus 2% (1/45) following MEL-140 ($P = 0{\cdot}05$). The causes of death included central nervous system bleeding in one patient; three had overwhelming sepsis and one died from complications following hepatorenal failure at d 30. TRM was 10% (3/31) following the second auto-SCT. In addition to the intensity of the conditioning regimen, the only statistically significant predictor for TRM was hypoalbuminaemia (albumin

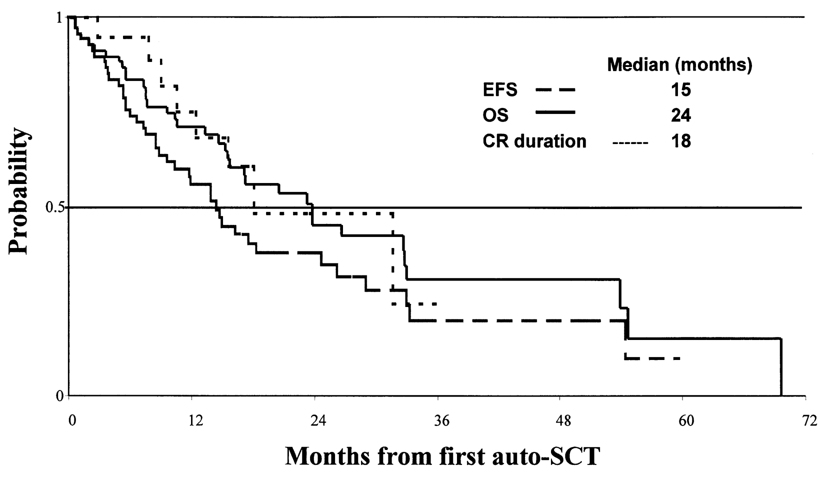

Fig 2. Aggregate overall survival (OS), event-free survival (EFS) and complete remission (CR) duration for patients ($n = 70$) receiving auto-SCT.

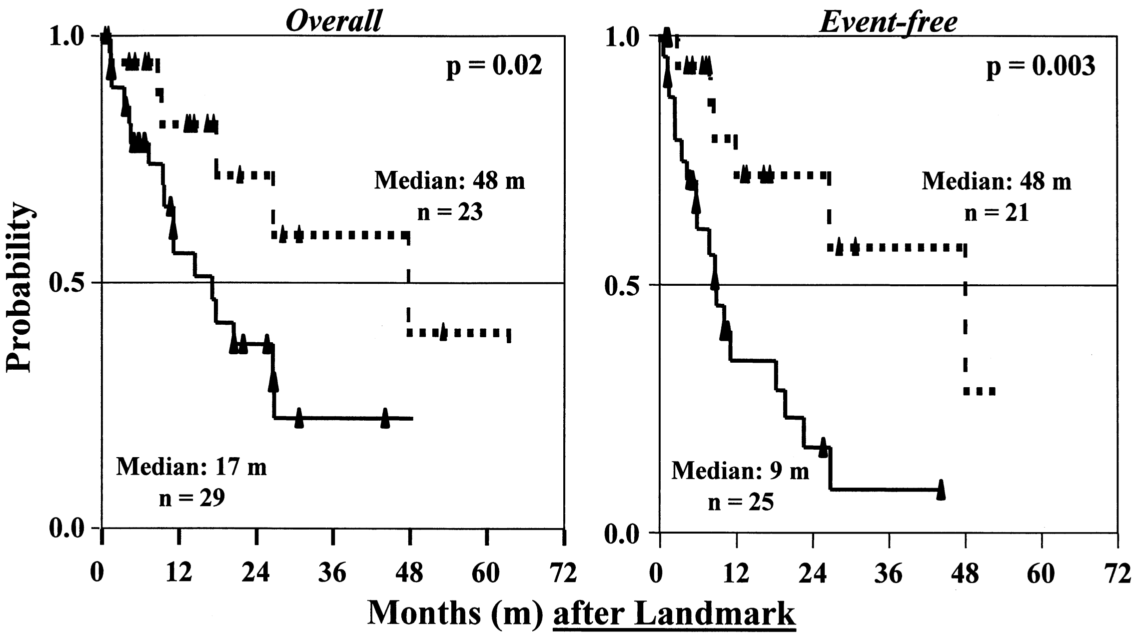

Fig 3. Effect of single (solid line) versus tandem (dashed line) auto-SCT on event-free (EFS) and overall survival (OS) after 6 months landmark analysis.

< 35 g/l, odds ratio = 7·9, $P = 0{\cdot}04$), reflecting a poor nutritional status and/or large volume disease.

Survival and prognostic factors

On multivariate analysis, OS and EFS were longer in patients with 12 months or less of prior CT (hazard ratio: 4·2 and 5·9, $P = 0{\cdot}001$ and 0·0004 respectively). CR rates were higher when patients were chemosensitive prior to auto-SCT (OR: 0·2, $P = 0{\cdot}012$). Neither the B2M level nor chromosome 13 abnormalities had significantly affected CR rates, CR durations, EFS or OS. EFS was better in patients who achieved either a CR (HR: 0·4, $P = 0{\cdot}03$)

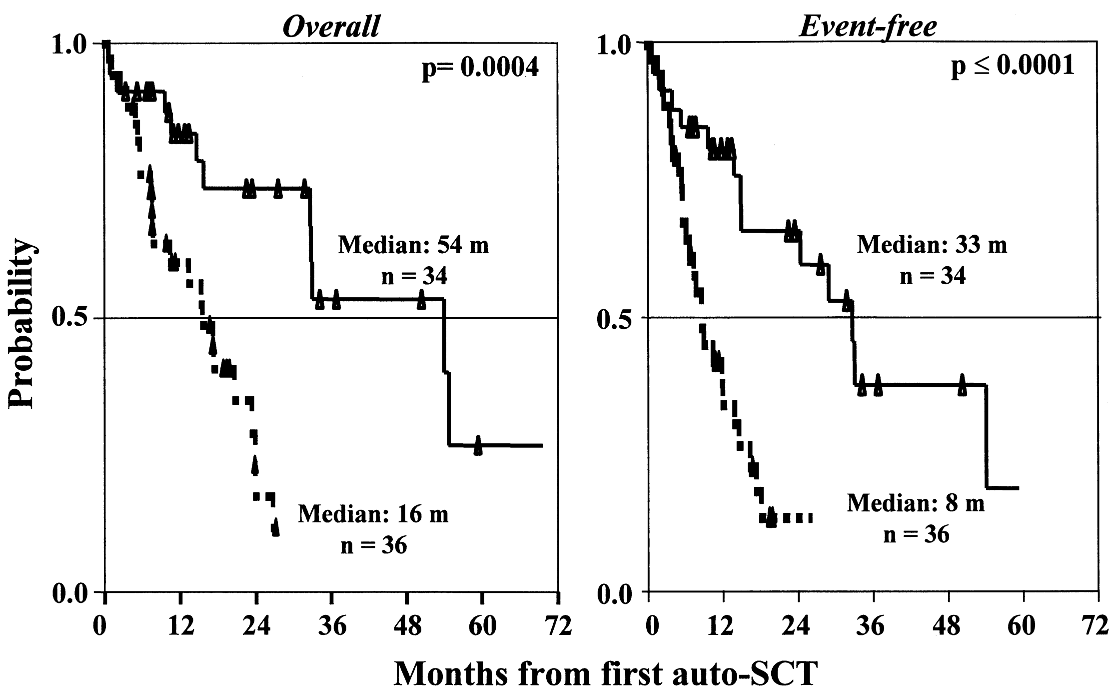

Fig 4. Effect of duration of prior chemotherapy (≤ 12 months, solid line, versus > 12 months, dashed line) on event-free (EFS) and overall survival (OS).

Table IV. Non-haematological toxicity following first auto-SCT.

Parameter	MEL-200 $n = 20$* (%)	MEL-140 $n = 30$* (%)	P-value
Mucositis	14 (70)	12 (40)	0·03
Diarrhoea	10 (50)	9 (30)	0·15
Cardiac	4 (20)	1 (3)	0·14
Pulmonary	3 (15)	0	0·05
Hepatic	2 (10)	0	0·15
Neurological	2 (10)	0	0·15
	$n = 25$* (%)	$n = 45$ (%)	
TRM	4 (16)	1 (2)	0·05

*Number of patients with adequate documentation of toxicity.
TRM, treatment-related mortality.

or received a second cycle of auto-SCT (HR: 0·2, $P = 0{\cdot}004$) (Table V).

DISCUSSION

Pilot studies have indicated that auto-SCT can be performed safely in selected elderly MM patients; the median age in these studies ranged from 65 to 70 years (Kusnierz-Glaz *et al*, 1997; Powles *et al*, 1997; Dumontet *et al*, 1998; Palumbo *et al*, 1999; Sirohi *et al*, 2000). However, there is very limited experience with this approach in patients over 70 years of age. The present study is the first report on the feasibility and toxicity of auto-SCT in large cohort of such MM patients addressing the impact of MEL-dose and tandem SCTs on the outcome.

Table V. Multivariate analysis.

Parameter	P*	Hazard ratio	95% CI†
Event-free survival			
Prior CT > 12 months	0·0004	5·9	2·2–15·9
Tandem SCT	0·004	0·2	0·09–0·6
CR	0·03	0·4	0·5–0·9
Chromosome 13	0·06	2·1	0·9–4·5
MEL-200 (for first SCT)	0·6	1·3	0·6–2·9
Age	0·8	1	0·2–1·1
Overall survival			
Prior CT > 12 months	0·003	4·2	1·6–11
Chromosome 13	0·3	1·5	0·7–3·3
Tandem SCT	0·5	0·7	0·3–1·8
Resistant disease	0·7	1·2	0·5–2·5
	P*	Odds ratio	95% CI†
Complete remission rate			
Resistant disease	0·01	0·2	0·06–0·7
Age	0·3	0·9	0·7–1·1
MEL-200 (first SCT)	0·6	0·7	0·2–2·5

*Based on Wald chi square (underlined data indicate significant values).
†Wald confidence interval.
Chromosome 13, abnormalities of chromosome 13; CT, chemotherapy; CR, complete remission; auto-SCT, autologous stem cell transplantation.

Early haematopoietic recovery is associated with lower TRM and toxicity following auto-SCT and is strongly determined by the number of CD-34$^+$ cells re-infused ($> 5 \times 10^6$/kg) (Tricot *et al*, 1995; Scheid *et al*, 1999). In our patients, we were able to mobilize adequate numbers of stem cells to support auto-SCT. Significantly higher CD-34$^+$ yields were collected following CY and G-CSF than with G-CSF alone. However, haematopoietic recovery post transplantation was similar regardless of the mobilization regimen. This observation was similar to our previous data comparing engraftment kinetics following stem cell infusion mobilized with G-CSF with or without CY in MM (Desikan *et al*, 1998). The numbers of stem cells mobilized were not different from those collected in younger patients and were significantly influenced by the duration of prior CT, particularly in patients who received more than 12 months of alkylating agents. This has been previously reported by our group with no difference in either the median number of CD-34$^+$ cells collected or time to engraftment between younger and older patients, when adjusted for duration of prior therapy (Guba *et al*, 1997; Desikan *et al*, 2001).

Mucositis, fever and diarrhoea were the main non-haematological toxicities noted. Multi-organ failure following sepsis post transplantation was the cause of death in three patients in the MEL-200 group. Low albumin had a significant impact on TRM. The co-morbidities associated with age and the special needs of the elderly (e.g. mental function, depression, mobility, family and social support, etc.) are important aspects in the care of these elderly patients (Haire *et al*, 1995; Courneya *et al*, 2000). Although not specifically addressed in this study, a comprehensive supportive care approach is essential to improve the outcome of these patients. Issues addressing quality of life were not evaluated in this study.

Although CR duration was longer in patients receiving MEL-200, they had a similar outcome to those receiving MEL-140 with regard to CR rate, EFS and OS. However, MEL-140 was associated with lower TRM. Palumbo *et al* (1999), in an attempt to deliver high-dose therapy to the majority of elderly newly diagnosed MM patients, evaluated an even lower dose of MEL 100 mg/m^2. Patients had a low severe mucositis rate and no TRM was reported. In addition, patients were able to tolerate up to three consecutive cycles of MEL. The CR was 19% after the first, 34% after the second and 45% after the third MEL-100. At a median follow-up of 30 months, 55% were alive in remission. Their clinical outcome was compared with that of 71 historical controls (median age, 64 years), selected from patients treated with melphalan and prednisone (MP) and matched for age and B2M. CR rate was 5% following MP. Median EFS was 34 months in the MEL-100 and 17·7 months in the MP group ($P < 0{\cdot}01$). Our present study confirms that intermediate-dose MEL can be administered safely to elderly patients with acceptable toxicity and a clinical outcome not too different from that seen in younger patients if adjusted for the significant prognostic factors.

The intensity of the conditioning regimen with the first auto-SCT did not affect the patient's ability to receive a second auto-SCT, which was delivered to 44%. High tumour burden, as reflected by high levels of B2M and IL-6, adversely affected the patient's ability to receive tandem auto-SCT. Additional causes for not receiving a second auto-SCT included lack of insurance cover and collection of inadequate numbers of stem cells for a second transplant. In order to deal with the bias in patient selection for second auto-SCT, we performed a landmark analysis. The administration of a second auto-SCT not only increased the CR rate to 27% but also positively affected the CR duration (27 versus 8 months), and EFS (48 versus 9 months) and OS (48 versus 17 months). Barlogie *et al* (1999) have shown similar results in the Total Therapy I trial, in which tandem SCT had a positive impact on CR rate, EFS and OS.

Duration of prior CT was an important prognostic factor for EFS and OS. Interestingly, B2M before transplantation, which is a confirmed prognostic variable in multiple studies, may lack significance in this elderly population (Merlini *et al*, 1993; Pasqualetti *et al*, 1996). B2M levels are higher in the elderly (60% of our patients had B2M level $>2{\cdot}5$ mg/l). This probably reflects an age-related decrease in creatinine clearance rather than a high tumour burden. Similarly, the presence of cytogenetic abnormalities that have been associated with inferior prognosis in younger patients did not affect the outcome in our study (Desikan *et al*, 2000). This may be as a result of the small number of patients and their diversity with regard to duration of prior therapy and number of auto-SCTs received in this study.

In summary, although this is a highly selected group of patients, our data support the concept that elderly (over 70 years of age) MM patients should not be excluded from the most effective treatment modality. Intermediate doses of MEL (140 in our study and 100 in the Torino study; Palumbo *et al*, 1999) are associated with less toxicity and have apparently equal efficacy with MEL-200 in these patients. Lower doses of MEL may enable the administration of repeated cycles of therapy, which has a greater impact on the outcome than the intensity of the conditioning regimen provided with the first auto-SCT. Auto-SCT should be performed early in the disease course before drug resistance develops and compromises the ability to collect an adequate number of stem cells to support tandem SCT. Elderly patients with low albumin had a higher TRM and may do better with even lower doses of MEL (70–100 mg/m^2). Dedicated teams and intensive supportive measures addressing the unique needs of the elderly are essential in improving the quality of life as well as the outcome and will require further investigations.

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