

Results of autologous stem cell transplant in multiple myeloma patients with renal failure

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Summary. Data are presented on 81 multiple myeloma (MM) patients with renal failure (creatinine $> 176.8 \mu\text{mol/l}$) at the time of autologous stem cell transplantation (auto-SCT), including 38 patients on dialysis. The median age was 53 years (range: 29–69) and 26% had received more than 12 months of prior chemotherapy. CD34^+ cells were mobilized with granulocyte colony-stimulating factor (G-CSF) alone ($n = 51$) or chemotherapy plus G-CSF ($n = 27$), yielding medians of 10 and $16 \times 10^6 \text{ CD34}^+$ cells/kg respectively ($P = 0.003$). Sixty patients (27 on dialysis) received melphalan 200 mg/m^2 (MEL-200). Because of excessive toxicity, the subsequent 21 patients (11 on dialysis) received MEL 140 mg/m^2 (MEL-140). Thirty-one patients (38%) completed tandem auto-SCT, including 11 on dialysis. Treatment-related mortality (TRM) was 6% and 13% after the first and second auto-SCT. Median times to absolute neutrophil count (ANC) $> 0.5 \times 10^9/\text{l}$ and to platelets $> 50 \times 10^9/\text{l}$ were 11 and 41 d respectively. Non-haematological toxicities included mucositis, pneumonitis, dysrhythmias and encephalopathy. At a median follow up of

31 months, 30 patients have died. Complete remission (CR) was achieved in 21 patients (26%) after first SCT and 31 patients (38%) after tandem SCT. Two patients discontinued dialysis after SCT. Median durations of complete remission (CR) and overall survival (OS) have not been reached; probabilities of event-free survival (EFS) and OS at 3 years were 48% and 55% respectively. Dialysis dependence and MEL dose did not affect EFS or OS. Sensitive disease prior to SCT, normal albumin level and younger age were independent prognostic factors for better OS. In conclusion, renal failure had no impact on the quality of stem cell collections and did not affect engraftment. MEL-140 had an acceptable toxicity and appeared equally effective as MEL-200. In the setting of renal failure, the role of auto-SCT early in the disease course and benefits of tandem SCT require further evaluation.

Keywords: multiple myeloma, renal failure, autologous stem cell transplantation.

Renal impairment is a presenting feature in 20% of multiple myeloma (MM) patients. In most studies, 2–3% of these patients require dialysis (DeFronzo *et al.*, 1978; Johnson *et al.*, 1990; Torra *et al.*, 1995; Magee *et al.*, 1998; Montseny *et al.*, 1998; Knudsen *et al.*, 2000). In early conventional chemotherapy (CT) trials, renal failure was an important predictor of poor prognosis (Durie & Salmon, 1975; Medical Research Council report, 1984). Subsequent studies have shown that poor prognosis is more a reflection of high tumour burden than renal function (Alexanian *et al.*, 1990). The response rates in MM patients with renal failure range from 40–50% and the median survival ranges from

4 months to 1 year. This is probably related to lower doses of CT administered to these patients and a high early treatment-related mortality (TRM) (Iggo *et al.*, 1989; Korzets *et al.*, 1990; Blade *et al.*, 1998). The degree and duration of renal failure significantly affect the chances of recovery of renal function. However, it has no impact on patients' responses to CT (Cosio *et al.*, 1981; Cohen *et al.*, 1984; Cavo *et al.*, 1986; Pozzi *et al.*, 1987; Korzets *et al.*, 1990; Innes *et al.*, 1994).

Several trials have shown that autologous stem cell transplantation (auto-SCT) is superior to CT in newly diagnosed MM patients 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). However, concerns about excessive toxicity and TRM led most centres to exclude renal failure patients from SCT

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trials, thus excluding a group of patients with a high tumour burden from the potential benefits of this procedure (Herget-Rosenthal *et al*, 2000). We have reported previously that renal failure patients, including those on dialysis, can receive high-dose melphalan (MEL). In our Total Therapy I, renal failure (creatinine $>176.8 \mu\text{mol/l}$) was reported in 9% of patients, and had no impact on EFS or OS (Barlogie *et al*, 1999). The pharmacokinetics of MEL in patients with renal dysfunction have not been extensively studied. A few studies have been published that address renal dysfunction and MEL pharmacokinetics (Gouyette *et al*, 1986; Tranchand *et al*, 1988; Samuels & Bitran, 1995; Tricot *et al*, 1996). However, these studies had very small sample sizes and offered conflicting conclusions.

This study reports the feasibility and safety of auto-SCT in a large group of MM patients with renal failure, including dialysis-dependent patients. Two different doses of MEL conditioning (200 mg/m^2 and 140 mg/m^2) were evaluated for their toxicity and impact on the clinical outcome.

PATIENTS AND METHODS

Between October 1996 and October 2000, 81 MM patients with renal failure received auto-SCT at the University of Arkansas for Medical Sciences. Renal failure was defined as creatinine $>176.8 \mu\text{mol/l}$, and included patients on dialysis. Inclusion criteria were age <70 years and acceptable cardiac (ejection fraction $>45\%$), pulmonary (DLCO $>60\%$) and hepatic (bilirubin and transaminases $<2 \times$ upper limit) function. Patients were excluded if a positive human immunodeficiency virus (HIV) was detected. All patients signed informed consent discussing the potential benefits and risks associated with stem cell collection and auto-SCT. The protocols and consent forms had been reviewed and approved by the Institutional Review Board.

Treatment. The first 60 patients received a MEL 200 mg/m^2 (MEL-200) preparative regimen. Because of excessive early toxicity after SCT, the dose was decreased to 140 mg/m^2 (MEL-140) in the subsequent 21 patients. According to the patient's tolerance and response to the first auto-SCT, a second auto-SCT was planned after 3–6 months. The dose of MEL for the second auto-SCT ranged from MEL-140 ($n = 7$) to MEL-200 ($n = 24$).

MEL was infused over 20 min. Patients in the MEL-200 group received $100 \text{ mg/m}^2/\text{d}$ for two consecutive days. MEL-140 was given in single infusion. Unmanipulated grafts were infused 48 h later. Granulocyte colony-stimulating factor (G-CSF), $5 \mu\text{g/kg/d}$, was given from d +1 until the neutrophil count was greater than $0.5 \times 10^9/\text{l}$ for two consecutive days. Blood cell count, electrolytes and renal function were followed daily. Oral levofloxacin, fluconazole and acyclovir were prescribed as antimicrobial prophylaxis with dose adjustments for creatinine clearance. Patients who developed neutropenic fever greater than 38°C received intravenous broad-spectrum coverage. Blood product support was administered to those with haemoglobin (Hb) concentration $<8 \text{ g/dl}$ or platelet count less than $20 \times 10^9/\text{l}$.

Nephrology consultants followed all patients on this protocol on a daily basis. Patients were dialysed before MEL infusions and again 24–48 h after stem cell infusion. The renal consultants determined fluid balance and electrolyte replacements.

Stem cells were collected following high-dose cyclophosphamide (CY) $2\text{--}4 \text{ g/m}^2$ intravenously with subsequent G-CSF at $10 \mu\text{g/kg/d}$ from d 3 to the last day of leukapheresis. Apheresis was initiated upon recovery of leucocytes to $2\text{--}10^9/\text{l}$. Heavily pretreated patients (more than 12 months of prior therapy or with low platelet count $<100 \times 10^9/\text{l}$) and those with minimal disease at mobilization received G-CSF alone at $10 \mu\text{g/kg/d}$ for 3 d before initiating leukapheresis. Dialysis was not interrupted during apheresis. Stem cell collections were performed before dialysis.

Statistical methods. All statistical analyses were conducted using the SAS version-8 software package. For baseline comparisons, the patients were divided into two groups defined by the preparative regimen for 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, OS and TRM. We examined the impact of MEL dose, dialysis dependence and tandem auto-SCT on outcome. Secondary endpoints analysed included the effect of the different mobilizing regimens on the CD34⁺ cell yield. EFS and OS were assessed using the method of Kaplan–Meier. 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 CR rate, 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. Overall response indicated more than 50% tumour mass reduction. TRM was defined as death for any reason within 60 d following auto-SCT. EFS and OS were defined as the time from first auto-SCT to progression and/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. Renal response defined as recovery of renal function.

RESULTS

Patients

The median age was 53 years (range: 29–69). Table I summarizes the characteristics of the 81 patients at first auto-SCT. Sixty patients received MEL-200 and 21 received MEL-140. There was no statistical difference between the two groups with respect to baseline disease characteristics (data not shown). Overall, 78% ($n = 63$) had Durie–Salmon clinical stage III-B and 67% ($n = 54$) were males. Light chain diseases accounted for 47% ($n = 38$) of the cases and IgA for 15% ($n = 12$). At the time of first auto-

Table I. Patient characteristics.

	n = 81 (%)
Male	54 (67)
Durie–Salmon stage IIIB	63 (78)
Light chain disease	38 (47)
IgA isotype	12 (15)
Albumin < 35 g/l	16 (20)
Calcium > 2.38 mmol/l	36 (44)
Haemoglobin < 10 g/dl	38 (47)
Platelet < 100 × 10 ⁹ /l	39 (48)
B2M > 10 mg/l	40 (49)
LDH > 300 U/l	6 (8)
Chromosome 13 Δ	9 (11)
Status at first auto-SCT	
Dialysis	38 (47)
> 12 months of chemotherapy	21 (26)
Sensitive disease	44 (56)
Resistant disease	34 (44)
First auto-SCT conditioning	
MEL-200 mg/m ²	60 (74)
MEL-140 mg/m ²	21 (26)
Tandem auto-SCT received	31 (38)

LDH, lactate dehydrogenase.

SCT, 44 patients (56%) had CT-sensitive and 34 patients (44%) had CT-resistant disease. Twenty-one patients (26%) had received ≥ 12 months prior CT. Nine patients had abnormalities of chromosome 13. Thirty-eight (47%) patients were on dialysis (36 on haemodialysis and two on peritoneal dialysis) at time of first auto-SCT; 27 of these patients received MEL-200 and 11 received MEL-140.

Thirty-one patients (38%) received tandem auto-SCT. Conditioning for second auto-SCT was MEL-200 in 24 patients and MEL-140 in seven patients, as determined by toxicity observed after the first auto-SCT. Twenty-three out of 31 patients received second auto-SCT within 6 months of the first. Thirteen dialysis patients proceeded with a second auto-SCT at a median of 4 months (range: 3–23) between the tandem auto-SCTs.

Stem cell mobilization and engraftment

Fifty-one patients were mobilized with G-CSF alone and 27 received CY and G-CSF. After 3–4 d of leukapheresis, an adequate number of CD34 cells (> 2 × 10⁶ CD34 cells/kg) was available to support at least one auto-SCT in all patients. Stem cell yield was affected significantly by mobilization regimen and duration of prior therapy (Table II). The median number of CD34 cells after CT plus G-CSF was 16 (range: 3–50) versus 10 × 10⁶/kg (range: 2.5–36) after G-CSF alone (*P* = 0.003). Patients who received ≤ 12 months of treatment had significantly higher CD34 cell yield than those receiving > 12 months of prior CT (median 12 versus 7 × 10⁶ CD34⁺ cell/kg; *P* = 0.01). Dialysis dependence had no effect on quality of stem cell collection.

Following the first auto-SCT, the median times to platelet

Table II. CD34 yield, analysed by mobilization regimen and months of prior therapy.

	n*	CD34 × 10 ⁶ /kg cells collected Median (range)	P†
Entire population	78	11 (2.5–50)	
Mobilization regimen			
G-CSF	51	10 (2.5–36)	
CY‡ & G-CSF	27	16 (3–50)	0.003
Duration of prior therapy			
< 12 months	58	12 (4–50)	
> 12 months	20	7 (2.5–31)	0.01

*Number of patients.

†Kruskal–Wallis test.

‡Cyclophosphamide.

recovery > 50 × 10⁹/l and absolute neutrophil count (ANC) > 0.5 × 10⁹/l were 41 d (range: 11–100+) and 11 d (range: 9–26) respectively. Dialysis and intensity of conditioning regimens did not affect the pace of engraftment.

Treatment-related toxicity

For the whole group, the median number of hospital days was 19 (range: 11–69 d). Early TRM with the first auto-SCT was 5% (1/21) in the MEL-140 group and 7% (4/60) in the MEL-200 group; (*P* = not significant). Four patients died following a second auto-SCT. Only two patients on dialysis died, one following the first and one following the second SCT. Low albumin (< 35 g/l) and presence of refractory disease at first auto-SCT were the main variables predicting an increased early TRM (*P* = 0.009 and 0.04 respectively). The main cause of death was multiorgan failure (*n* = 6).

Severe toxicities (> grade II) associated with the first auto-SCT are presented in Table III. Toxicities were grouped and analysed by the MEL-dose and the requirement for dialysis. All patients had grade III–IV neutropenia and thrombocytopenia. Fever occurred in all patients; however, documented bacterial infections developed in half of the patients (48%). Diarrhoea and vomiting affected two-thirds of the patients. Mucositis was present in 93% of the MEL-200 patients versus 67% in the MEL-140 (*P* = 0.04). Patients on dialysis had no statistically significant increased incidence of mucositis (77% versus 94%) (*P* = 0.2). Pulmonary complications were significantly more frequent with MEL-200 than with MEL-140 (57% versus 17%; *P* = 0.007) and in dialysis-dependent patients (53% versus 19%, *P* = 0.02). Eight of these patients required ventilator support. Cardiac complications, specifically atrial dysrhythmias, and neurological complications, particularly encephalopathy, were more frequent in the MEL-200 group. The latter complication was more prominent in dialysis-dependent patients (47% versus 6%, *P* = 0.005). Skin rash was

Table III. Effect of melphalan dose and haemodialysis on toxicity.*

Side-effects	MEL-140 <i>n</i> = 18† (%)	MEL-200 <i>n</i> = 28† (%)	<i>P</i>	HD <i>n</i> = 30† (%)	No HD <i>n</i> = 16† (%)	<i>P</i>
Vomiting	13 (72)	22 (79)	0.7	21 (70)	14 (88)	0.3
Mucositis	12 (67)	26 (93)	0.04	23 (77)	15 (94)	0.2
Diarrhoea	8 (44)	19 (68)	0.1	16 (53)	11 (69)	0.3
Infections	10 (56)	12 (43)	0.4	12 (40)	10 (62)	0.15
Pulmonary	3 (17)	16 (57)	0.007	16 (53)	3 (19)	0.02
Hypotension	1 (5)	7 (25)	0.12	6 (20)	2 (12)	0.7
Dysrhythmia	0	6 (21)	0.07	5 (17)	1 (6)	0.6
Neurological	5 (27)	10 (36)	0.6	14 (47)	1 (6)	0.005
Skin rash	5 (27)	10 (36)	0.6	3 (10)	12 (75)	< 0.0001
TRM	<i>n</i> = 21 1 (5)	<i>n</i> = 60 4(6)	0.4	<i>n</i> = 38 2(5)	<i>n</i> = 43 7(16)	0.2

*Grade II and higher by NCI criteria.

†Number of patients with adequate documentation of toxicity.

MEL, melphalan; HD, haemodialysis; TRM, treatment-related mortality.

significantly more common in non-dialysis dependent patients (10% versus 75%, $P = < 0.0001$).

Clinical response

As of October 30, 2000, 30 patients had died; the median follow up for alive patients was 31 months (range: 3–52); 3-year EFS and OS (\pm SE) were 48% (\pm 10) and 55% (\pm 9) respectively. In the whole group of previously treated and newly diagnosed patients, CR was achieved in 31 patients with a median CR duration of > 48 months, EFS was 23 months and median OS was > 52 months (Fig 1).

Overall, CR was achieved in 21 patients (26%) after the first auto-SCT and 31 patients (38%) after tandem auto-SCTs. The intensity of the conditioning regimen at first auto-SCT did not

affect CR rate (35% following MEL-200 and 33% following MEL-140, $P = 0.9$). Similarly, CR rate was not significantly affected by dialysis dependence (37% in dialysis patients versus 33% in the non-dialysis group; $P = 0.7$). Tandem SCT did not significantly improve EFS/OS compared with single auto-SCT ($P = 0.6/0.6$). In fact, patients receiving a second auto-SCT tended to have a lower OS than patients receiving a single auto-SCT (Fig 2). MEL-200 for the first auto-SCT had a marginal impact on EFS but not OS compared with MEL-140 (Fig 3). Median EFS/OS was 23/50 months for patients who had received < 12 months of prior CT versus 13/20 months for patients with > 12 months of prior CT ($P = 0.3/0.2$ respectively). Dialysis-dependent and non-dependent patients had similar EFS/OS ($P = 0.8/0.4$) (Fig 4).

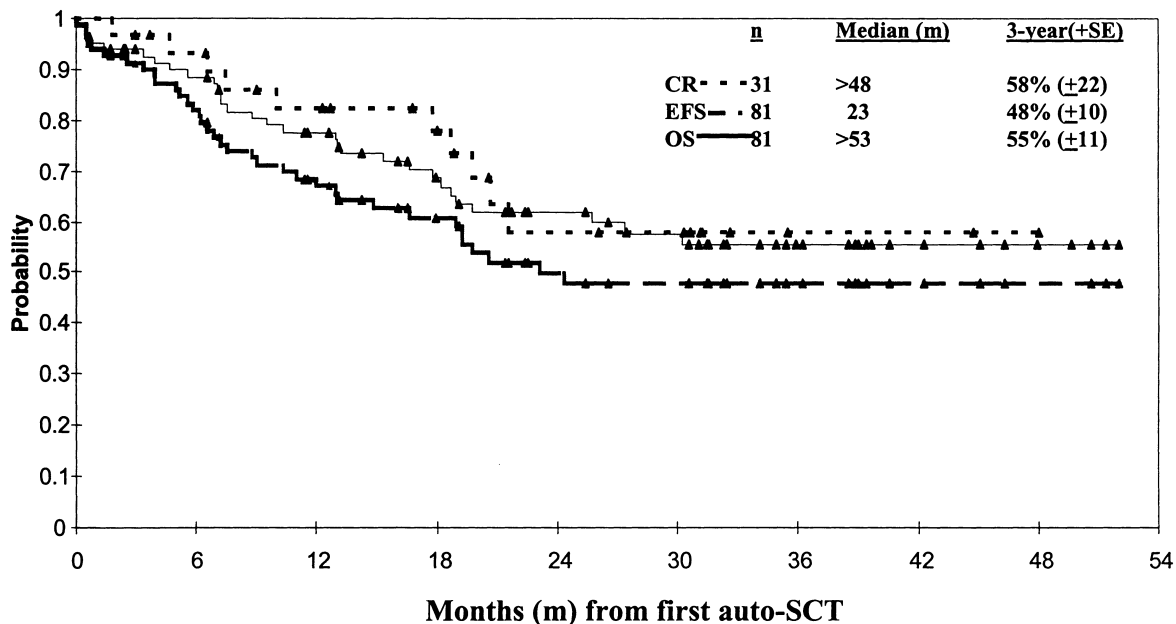


Fig 1. Actuarial survival for myeloma patients with renal failure after auto-SCT.

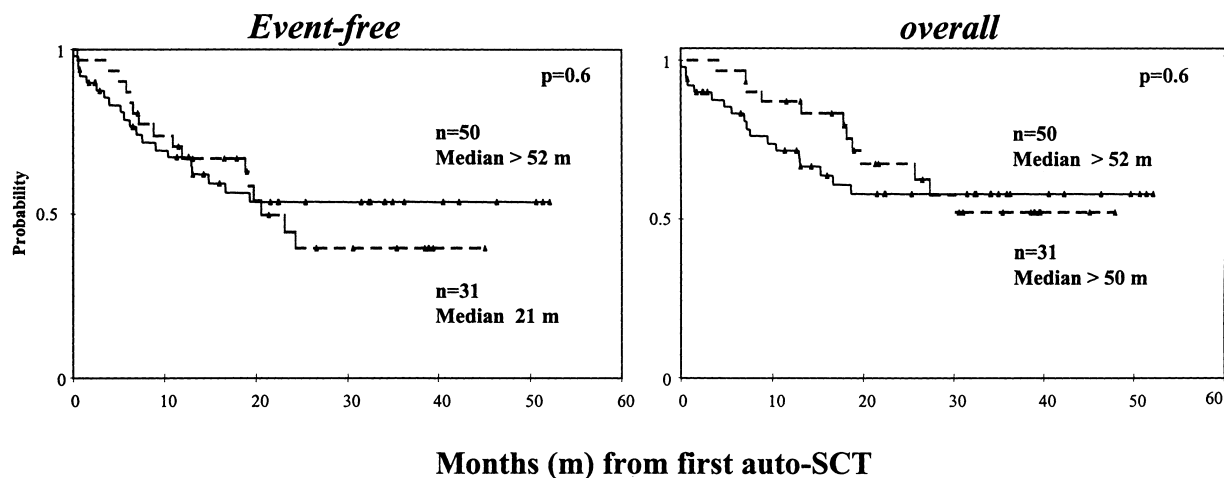


Fig 2. Actuarial survival according to the number of auto-SCT (single (n = 50) – versus tandem (n = 31) ---). Tandem SCT did not significantly improve EFS/OS compared with single auto-SCT; in fact patients receiving a second auto-SCT had a lower OS.

Survival and prognostic factors on multivariate analysis

On multivariate analysis, OS and EFS were longer in patients with CT-sensitive disease at the time of first auto-SCT (Table IV). OS was significantly affected by low albumin and older age. Chromosome 13 abnormalities had a significant impact on EFS but not OS. The intensity of the conditioning regimen (MEL-200 versus MEL-140) and dialysis dependence had no impact on EFS or OS.

DISCUSSION

The prognosis of MM patients treated with standard CT in the setting of renal failure has been poor. There are several reports of auto-SCT in MM patients with renal failure showing that the procedure is safe and effective (Pecherstorfer *et al*, 1994; Tricot *et al*, 1996; Ballester *et al*, 1997; Krejci *et al*, 1997; Rebibou *et al*, 1997; Reiter *et al*, 1999; Tosi *et al*, 2000). Our study is the first prospective analysis of a large number of MM patients showing the safety of

auto-SCT in the setting of renal failure, including haemodialysis.

The non-haematological toxicity associated with MEL-200 was significantly higher than with MEL-140. Encephalopathy progressing to coma was a unique observation in some renal failure patients, particularly those on dialysis. The exact cause is unclear, but infections, metabolic changes and altered drug metabolism are probably all contributory factors (Schuh *et al*, 1999). Renal failure patients tend to have a low serum albumin. This may affect MEL-pharmacokinetics as 60% of the drug is bound to plasma proteins, mainly albumin (Chang *et al*, 1978; Gera *et al*, 1989). Low albumin and the high concentration of the free drug increased overall toxicity and mortality and was an independent factor affecting OS.

Our patients were able to mobilize adequate numbers of stem cells to support auto-SCT with no difference in yields between dialysis-dependent and independent patients. Significantly higher CD34⁺ yields were collected following CY

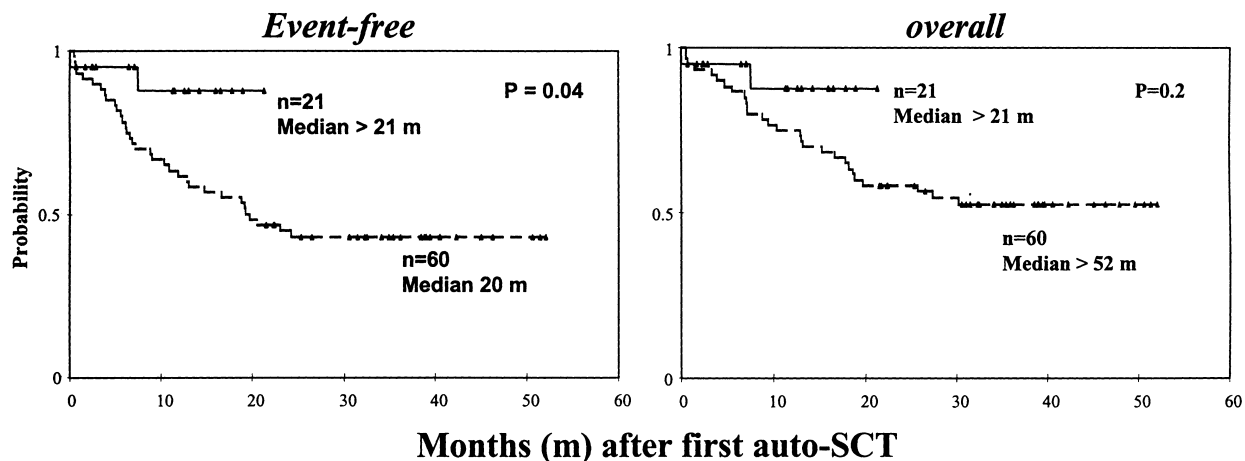


Fig 3. Actuarial survival according to the dose of MEL (200 (n = 60) --- versus 140 (n = 21) –) at the first SCT. Mel-200 for the first transplant had a marginal impact on EFS and OS compared with Mel-140

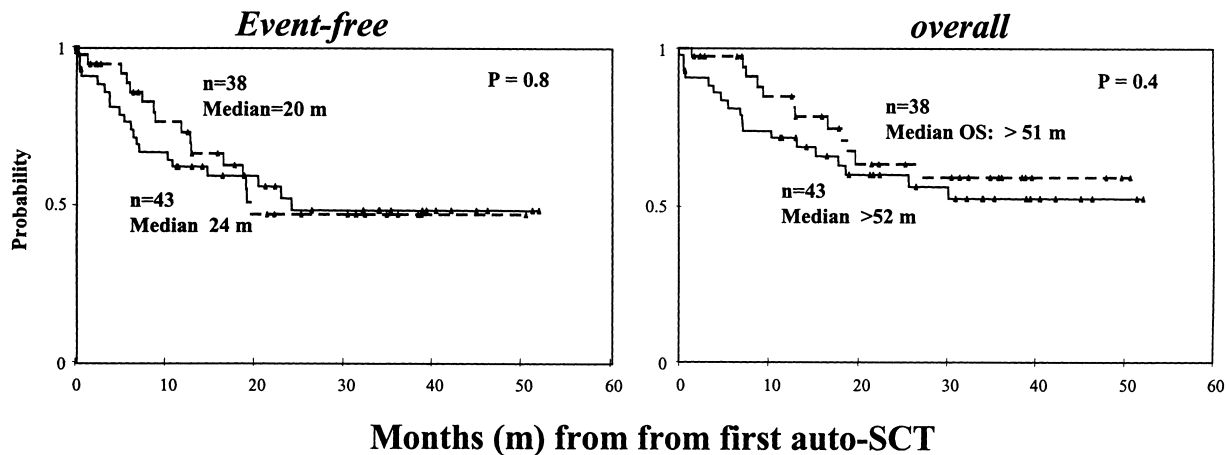


Fig 4. Actuarial survival after auto-SCT according to dialysis dependency (haemodialysis (n = 38) --- versus no haemodialysis (n = 43) -). Dialysis dependency did not affect the outcome (EFS/OS) in patients undergoing auto-SCT.

and G-CSF than with G-CSF alone, which was mostly a reflection of haematopoietic reserve, as most heavily pretreated patients received G-CSF alone. However, engraftment kinetics were similar regardless of the mobilization regimen (data not shown). The numbers of stem cells collected were significantly influenced by the duration of prior CT, as previously reported (Desikan *et al.*, 2001).

Some standard CT trials have shown that recovery of renal function in MM patients is associated with improved survival (Pozzi *et al.*, 1987; Rota *et al.*, 1987; Tapson *et al.*, 1988; Alexanian *et al.*, 1990), while others suggest that dialysis *per se* does not impair survival (Cohen *et al.*, 1984; Cavo *et al.*, 1986; Blade *et al.*, 1998). In our study, only two dialysis patients recovered partial renal function. As 47% of our patients had light chain deposition disease and 26% had more than 12 months of renal impairment, it is unlikely that they will recover their renal function (Confalonieri *et al.*, 1988). In our study, dialysis had no affect on response to

therapy, EFS or OS. Whether the use of SCT to achieve maximum cyto-reduction, early in the disease course, can stop renal damage and increase the chances of recovery of renal function should be evaluated prospectively.

The response rate to standard CT in MM patients with renal failure ranges from 35% to 50%, which is significantly lower than in patients with normal renal function. (Misiani *et al.*, 1987; Iggo *et al.*, 1989; Korzets *et al.*, 1990; Blade *et al.*, 1998). Few if any CR were observed with CT (Durie *et al.*, 1986; Baldini *et al.*, 1991; Zervas *et al.*, 2001). In our patients, the CR rate was 26% and 38% after the first and second SCT respectively. This is similar to CR rates of 22–45% for patients with normal renal function receiving single and tandem SCT respectively (Attal *et al.*, 1996; Powles *et al.*, 1997; Barlogie *et al.*, 1999).

Median survival with CT ranges from 4 months to 1 year (Medical Research Council report, 1984; Pozzi *et al.*, 1987; Irish *et al.*, 1997; Magee *et al.*, 1998) in MM patients with renal failure versus a median survival of 3 years in MM patients with normal renal function (Zervas *et al.*, 2001). Median OS in our patients was 52+ months, which was similar to patients with normal renal function receiving SCT. Sensitive disease, low albumin and older age were significant and independent poor prognostic factors for OS. Beta-2-microglobulin (B2M), a significant prognostic variable in MM patients, lacks significance in renal failure patients as 90% of our patients had B2M levels > 10 mg/l.

MEL-140 was well tolerated and had outcomes similar to MEL-200 with regard to CR rate, EFS and OS. Only 38% of the patients received the planned second auto-SCT. This is almost half of what is expected in MM patients with normal renal function on tandem SCT protocols (Barlogie *et al.*, 1999). Causes for not receiving tandem SCT included significant toxicity with the first SCT, lack of insurance coverage and inadequate numbers of stem cells. In renal failure patients, apart from modest increase in CR rate, tandem SCT did not significantly improve EFS or OS. This is in contrast to the results reported in MM patients with normal renal function (Desikan *et al.*, 2000).

Table IV. Multivariate analysis.

Parameter	P*	Hazard ratio	95% CI
Event-free survival			
Sensitive disease	0.001	0.3	0.2–0.6
Chromosome 13	0.02	2.7	1.1–6.5
MEL-200†	0.09	3.5	0.8–15
Haemodialysis	0.7	0.8	0.4–1.7
Overall survival			
Sensitive disease	0.001	0.3	0.1–0.6
Albumin	0.003	0.4	0.2–0.7
Age	0.003	1.1	1.0–1.1
MEL-200†	0.2	2.5	0.6–11
Haemodialysis	0.9	0.9	0.4–2.08

*Based on Wald chi square.

†MEL-200, melphalan dose at first auto-SCT. CI, confidence interval.

In summary, our data show that renal failure should not be an exclusion criterion from the most effective treatment modality for MM, auto-SCT. Intermediate dose MEL-140 is associated with less toxicity than and equal efficacy to MEL-200. Auto-SCT should be performed early in the disease course before renal failure becomes irreversible. Renal failure patients with low albumin had a higher TRM and may do better with even lower doses of MEL (70–100 mg/m²).

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