

## ORIGINAL ARTICLE

# High-dose melphalan (200 mg/m<sup>2</sup>) supported by autologous stem cell transplantation is safe and effective in elderly (≥65 years) myeloma patients: comparison with younger patients treated on the same protocol

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Limited information is available on the feasibility and efficacy of autologous stem cell transplantation (ASCT) in multiple myeloma (MM) patients >65 years of age. In 1995–2005, 22 myeloma patients ≥65 years (median 68, eight ≥70) and 79 patients <65 years (median 57) were included in an identical treatment protocol. The first progenitor cell mobilization with cyclophosphamide plus granulocyte-colony stimulating factor (G-CSF) was successful in 95 and 96% of the patients, respectively. To date, 92 patients have received MEL (melphalan) 200 mg/m<sup>2</sup> supported by ASCT. No early treatment-related deaths were observed among 22 elderly patients, whereas one younger patient died early. Engraftment and the need for supportive care were comparable between groups. The elderly patients tended to have more WHO grade 3–4 oral or gastrointestinal toxicity when compared to the younger patients (45 vs 23%, *P* = 0.06). After ASCT, a complete response was observed in 44% of the elderly patients and 36% of the younger patients, respectively. No difference was observed between these age groups in progression-free survival (23 vs 21 months) or overall survival (57 vs 66 months) after ASCT. We conclude that MEL200 is a safe and efficacious treatment in selected elderly myeloma patients.

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prednisolone. Advanced age has been considered as a poor prognostic factor with a median survival of 3 years or less.<sup>1,2</sup> However, clinical and biological features between younger and elderly patients are comparable.<sup>3</sup> Therefore, the poorer prognosis of elderly patients may be due to poorer tolerance to standard chemotherapy, although concomitant medical conditions without doubt also play a role in terms of overall survival.

High-dose therapy (HDT) supported by autologous stem cell transplantation (ASCT) has become a standard treatment in patients with MM based on randomized clinical trials<sup>4,5</sup> as well as matched comparisons.<sup>6,7</sup> Conventionally, the upper age limit for this form of therapy has been around 65 years due to anticipated higher treatment-related toxicities in elderly patients. Limited published data are available on the feasibility and efficacy of ASCT in myeloma patients more than 60 or 65 years of age.<sup>8–10</sup> High-dose melphalan (HD-MEL) (200 mg/m<sup>2</sup>) has become the standard high-dose regimen (HDT) in patients with MM.<sup>11</sup> In some series an attenuated dose of MEL (100–140 mg/m<sup>2</sup>) has been used in elderly myeloma patients in order to reduce toxicity.<sup>9,12</sup> As the dose–response relationship of MEL is steep,<sup>13,14</sup> higher MEL doses might also give better outcomes in elderly myeloma patients provided that the treatment is reasonably well-tolerated.

We evaluated the feasibility and efficacy of MEL 200 mg/m<sup>2</sup> (MEL200) followed by autologous blood stem cell infusion in myeloma patients aged 65 years or more and compared these issues with patients aged <65 treated on the same HDT protocol in 1995–2005.

## Introduction

The majority of patients with multiple myeloma (MM) are >65 years old at diagnosis. Conventionally, these patients have been treated with a combination of melphalan and

## Patients and methods

### Patients

Between January 1995 and September 2005, 101 myeloma patients were included on the ASCT protocol at the Department of Medicine, Kuopio University Hospital, Kuopio, Finland. The initial treatment was VAD (vincristine, doxorubicin, dexamethasone) in 98 patients; these patients were then enrolled onto the HDT protocol. Three patients were included into HDT protocols later during the disease course. All patients received progenitor cell

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mobilization with cyclophosphamide (CY) followed by G-CSF ( $5 \mu\text{g}/\text{kg}/\text{day}$ ) and underwent progenitor cell apheresis. The basic characteristics of these patient groups are presented in Table 1. Characteristics of the patients at the time of progenitor cell mobilization are presented in Table 2.

### High-dose therapy protocol

**Progenitor cell mobilization and apheresis.** Initially, the mobilization protocol consisted of CY  $4 \text{ g}/\text{m}^2$  as a 90 min infusion plus MESNA on day 0, followed by G-CSF  $5 \mu\text{g}/\text{kg}/\text{day}$  s.c. from day +2 until the end of progenitor cell apheresis or until mobilization failure ( $N=55$ ). From 2002 onwards, low-dose ( $2 \text{ g}/\text{m}^2$ ) CY followed by G-CSF,<sup>15</sup> was used in myeloma patients who achieved at least a partial response (PR) with induction therapy ( $N=46$ ). In patients refractory to induction therapy and those with extensive

prior irradiation, CY  $4 \text{ g}/\text{m}^2$  plus G-CSF was used for mobilization.

Patients were admitted to our department on day +8 and the first B-CD34<sup>+</sup> count was estimated on day +9 provided that the leukocyte count was  $>0.5 \times 10^9/\text{l}$ . The decision to start progenitor cell apheresis was based mainly on B-CD34<sup>+</sup> counts. In patients with morning counts  $>20 \times 10^6/\text{l}$ , apheresis was started on the same day. In patients with B-CD34<sup>+</sup> counts  $5\text{--}20 \times 10^6/\text{l}$ , apheresis was started on an individual basis, taking into account both leukocyte count and differential in addition to B-CD34<sup>+</sup> count.

Aphereses were performed with the COBE SPECTRA<sup>R</sup> cell separator (Denver, CO, USA). A volume of 10–14 l of blood was processed over 3–4 h. Grafts containing at least  $2 \times 10^6/\text{kg}$  CD34<sup>+</sup> cells were considered sufficient to proceed to ASCT. In hard-to-mobilize patients (at least three collections), a graft containing at least  $1.5 \times 10^6/\text{kg}$  CD34<sup>+</sup> cells was considered sufficient to proceed to HDT. Patients who mobilized less CD34<sup>+</sup> cells were regarded as mobilization failures and were considered for re-mobilization on an individual basis.

The collection product was frozen in 10% DMSO (final concentration) under computer control with a cryopreservation device (Kryo 10<sup>R</sup> Planer, Sunbury-on-Thames, UK). Frozen products were stored at  $-140^\circ\text{C}$  in an electric freezer with liquid nitrogen back-up.

**High-dose therapy and supportive care.** Previously, central venous catheters were used in patients undergoing stem cell transplantation but since 2003 peripheral catheters have been used provided that peripheral veins are adequate. HDT consisted of melphalan  $200 \text{ mg}/\text{m}^2$  (MEL200) in a 15–30 min infusion on day –2, followed by progenitor cell infusion on day 0. Ten patients received amifostine with an intended dose of  $910 \text{ mg}/\text{m}^2$  just before MEL200 in a phase II protocol.<sup>16</sup> The proportion of patients who received amifostine pretreatment was comparable between age groups (9% in the elderly vs 11% in the younger age group). G-CSF  $5 \mu\text{g}/\text{kg}/\text{day}$  s.c. was started initially on day +2, but from 2002 onwards on day +4 and continued until neutrophils were  $>1 \times 10^9/\text{l}$ . From 2004 onwards patients with excellent grafts ( $>5 \times 10^6/\text{kg}$  CD34<sup>+</sup> cells) who were clinically stable on day +5 did not receive G-CSF at all. Altogether 86 out of 92 patients (94%) who received HD-MEL supported by ASCT received G-CSF after stem cell infusion. The proportion of patients receiving G-CSF was comparable in patients <65 years old and the elderly patients (97 vs 87%). For prophylaxis against *Pneumocystis carinii*, cotrimoxazole was used for 4 months after ASCT.

From day +4 blood cell counts were measured daily and serum C-reactive protein (CRP) three times per week unless otherwise clinically indicated. Serum creatinine and electrolytes were measured routinely three times a week and liver enzymes and bilirubin twice a week. In cases of neutropenic fever ( $>38^\circ\text{C}$ ), 2–3 blood cultures were taken from peripheral veins and a combination of betalactam and aminoglycoside was started. Oral fluconazole ( $200 \text{ mg}/\text{day}$ ) was used for mucosal symptoms during neutropenia. Red blood cell concentrates were given to keep the haemoglobin

**Table 1** Characteristics of 101 myeloma patients included in the HDT protocol from 1995–2005

	<65 years	≥65 years
No. of patients	79	22
Age, median (range)	57 (39–64)	68 (65–73)
<b>Gender</b>		
Male	45 (57%)	12 (55%)
Female	34 (43%)	10 (45%)
<b>Myeloma subtype</b>		
IgG	45 (57%)	12 (55%)
IgA	22 (28%)	4 (18%)
IgM	1 (1%)	0
Light chain	9 (11%)	6 (27%)
Biclonal	1 (1%)	0
Non-secretory	1 (1%)	0
Kappa/lambda	52/26 (66/33%)	14/8 (64/36%)
<b>Durie–Salmon stage at the start of therapy</b>		
I	11 (14%)	1 (5%)
II	27 (33%)	10 (45%)
III	41 (52%)	11 (50%)
a/b	72/7 (91/9%)	18/4 (82/18%)

**Table 2** Patient characteristics of 101 myeloma patients at the time of progenitor cell mobilization

	<65 years (N = 79)	≥65 years (N = 22)
Months from dg to mobilization, median (range)	5 (3–30)	5 (3–21)
No. of CT cycles, median (range)	4 (3–12)	4 (3–6)
No. of patients with MEL-containing therapy	9 (11%)	3 (14%)
RT before mobilization	12 (15%)	4 (18%)
<b>Disease status at mobilization</b>		
CR	6 (8%)	3 (14%)
PR	55 (70%)	16 (73%)
NR	18 (21%)	3 (14%)

Abbreviations: CT = chemotherapy; MEL = melphalan; RT = radiotherapy; CR = complete response; PR = partial response; NR = non-responder.

level >80 g/l and platelet concentrates were given to keep the platelet count >20 × 10<sup>9</sup>/l. For assessment of toxicity from HDT, the WHO grading<sup>17</sup> was used. Only toxicity grades 3–4 were taken into account.

Alpha-interferon (IFN) was started 2–3 months after ASCT based on the decision by the local physician provided that stable engraftment had occurred. Altogether 31 younger patients (44%) and six elderly patients (28%) received IFN post transplant.

#### Follow-up after HDT

Patients were followed at their own hospitals after HDT. Follow-up data including treatment response, time to progression and status at last visit were collected in September 2005. A patient was considered evaluable for treatment response after HDT if at least 6 months had elapsed since HDT.

#### Definition of treatment response and progression

Complete response was defined as disappearance of the paraprotein from serum or urine on electrophoresis, respectively. Immunofixation (IF) was not routinely used in all hospitals during the study period and IF negativity was thus not used as a criterion for complete response. Partial response was defined as a decrease in paraprotein of at least 50% in serum from the pretreatment value, or at least a 90% decrease in urinary of paraprotein or <200 mg/day.<sup>18</sup> All other outcomes were defined as non-responders.

Progression was defined as a reappearance of paraprotein in serum or urine, observed on two consecutive measurements in patients who had previously achieved complete response. In patients who had achieved a partial response or in non-responders, an increase in serum or urine paraprotein of at least 25% from the nadir after ASCT was considered progression.<sup>18</sup>

#### Statistical analysis

All analyses were performed using the SPSS 11.0 for Windows (SPSS, Chicago, IL, USA). Means between the groups were compared using the Mann–Whitney *U*-test. The  $\chi^2$ -test was used to compare nominal data between groups. Progression-free survival (PFS) and overall survival (OS) were computed from the date of ASCT with the Kaplan–Meier method. Patients who received reduced-intensity conditioned allografts in complete or partial response following an autograft were excluded from the analysis of PFS, as were patients who died from causes

other than myeloma treatment provided that they had not experienced disease progression before death.

## Results

#### Progenitor cell mobilization and collection

The first mobilization attempt was successful ( $\geq 1.5 \times 10^6$ /kg CD34<sup>+</sup> cells collected) in 97 patients (96%). Two patients were remobilized and in both the minimum collection target was reached; they proceeded to HDT with stem cell support. Two younger patients had refractory disease at the time of mobilization failure and were not considered candidates for re-mobilization. There were no statistically significant differences in terms of mobilization efficiency between the age groups (Table 3).

#### Engraftment and need for supportive care during HDT

All patients experienced engraftment after HD-MEL. Time to engraftment and need for supportive care were comparable between elderly patients and patients <65 years of age (Table 4).

#### Infectious complications after HDT

Although febrile neutropenia was observed in about 70% of patients in both age groups (Table 5), culture-proven septicemias were far less common (9%). Blood culture findings included *Pseudomonas aeruginosa* (*N* = 2), *Klebsiella pneumoniae* (*N* = 2) *Staphylococcus epidermidis* (*N* = 2), *Staphylococcus aureus* (*N* = 1), and *Streptococcus alfa-haemolyticus* (*N* = 1). One younger patient with

**Table 4** Engraftment and need for supportive care in myeloma patients who received high-dose therapy (MEL200) with progenitor cell support in 1995–2005. Values are medians (range in parenthesis)

	<65 ( <i>N</i> = 70)	≥65 years ( <i>N</i> = 22)	P-value
Days to neutrophils >0.5 × 10 <sup>9</sup> /l	11 (7–14)	11 (9–25)	NS
Days to platelets >20 × 10 <sup>9</sup> /l	12 (9–24)	12 (9–23)	NS
No. days with G-CSF	8 (0–12)	7 (0–12)	NS
No. of platelet units transfused	8 (0–85)	8 (0–24)	NS
No. of RBC units transfused	0 (0–19)	0 (0–4)	NS
Days on parenteral antibiotics	6 (0–32)	5 (0–25)	NS
In-hospital days during HDT	16 (13–39)	18 (14–32)	NS

Abbreviations: G-CSF = granulocyte colony-stimulating factor; RBC = red blood cell; HDT = high-dose therapy.

**Table 3** Progenitor cell mobilization and apheresis in 101 myeloma patients

	<65 years ( <i>N</i> = 79)	≥65 years ( <i>N</i> = 22)	P-value
Peak B-CD34 <sup>+</sup> (× 10 <sup>6</sup> /l) after mobilization, median (range)	47 (<1–546)	63 (4–274)	NS
No. patients with peak B-CD34 <sup>+</sup> <20 (× 10 <sup>6</sup> /l)	7 (9%)	2 (9%)	NS
No. of aphereses, median (range)	1 (0–4)	1 (1–3)	NS
No. of patients with a single apheresis yielding ≥2 × 10 <sup>6</sup> /kg CD34 <sup>+</sup> cells	64 (81%)	19 (86%)	NS
No. CD34 <sup>+</sup> cells collected, median (range) <sup>a</sup>	4.5 (1.2–47.4)	5.2 (0.4–20.0)	NS
CD34 <sup>+</sup> selection	4 (5%)	0	NS
Mobilization failure	3 (4%)	1 (5%)	NS

<sup>a</sup>Apheresis was not started in two patients due to poor mobilization.

**Table 5** Toxicity of HDT in myeloma patients transplanted in 1995–2005

	< 65 years (N = 70)	≥65 years (N = 22)	P-value
No. of patients with neutropenic fever	51 (70%)	16 (73%)	NS
No. of patients with positive blood culture	7 (10%)	1 (5%)	NS
Peak CRP mg/l, median (range)	56 (5–360)	54 (5–200)	NS
WHO grade 3–4 oral or gastrointestinal toxicity	16 (23%)	10 (45%)	0.06
ICU admission	2 (2.8%)	0	NS
Early death (<100 days)	1 (1.4%)	0	NS

Abbreviations: CRP = C reactive protein; WHO = World Health Organization; ICU = intensive care unit.

*Pseudomonas* septicemia developed multi-organ failure but recovered within a week of therapy in intensive care.

One younger patient with therapy-refractory pneumonia was found to have pulmonary aspergillosis at autopsy. No other fungal infections were observed.

#### Toxicity associated with high-dose therapy

No elderly patients ( $N=22$ ) died due to early treatment-related causes, whereas one out of 70 younger patients died due to fungal pneumonia (TRM 1.4%). WHO grade > 3–4 oral or gastrointestinal toxicity was more common in the elderly patients (45 vs 23%,  $P=0.06$ ) (Table 5). The most common WHO 3–4 toxicity in the whole patient population was diarrhea (15 patients, 17%) followed by oral mucositis (12 patients, 13%). No cases of grade 3–4 cardiac complications were observed in elderly patients. The median peak CRP value was comparable in the younger and elderly patients (56 vs 54 mg/l) (Table 5).

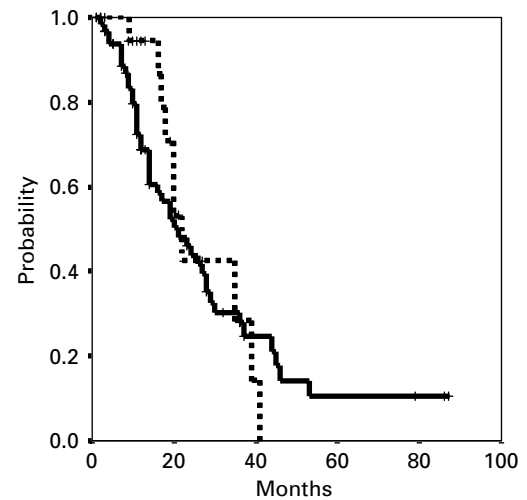
#### Outcome after autologous stem cell transplantation

One younger patient died early from early treatment-related causes and was not evaluable for treatment response. Four elderly patients and eight patients <65 years of age had a follow-up of less than 6 months from HDT and were thus not evaluable for treatment response.

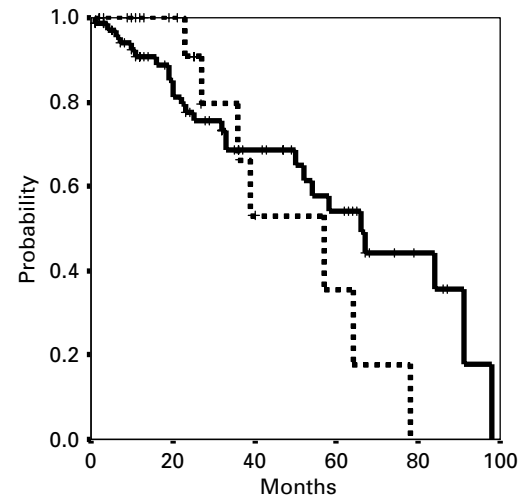
Eighteen elderly patients (82%) were evaluable for treatment response. Eight patients (44%) were in complete response after ASCT, and nine patients (50%) achieved a partial response. Sixty-one patients younger than 65 years (87%) were evaluable for treatment response. Altogether 22 patients (36%) were in complete remission after HDT and another 23 patients (38%) had a partial response.

To date, 10 patients > 65 years old (45%) have relapsed or progressed. The actuarial median PFS is 23 months from ASCT (Figure 1). On the other hand, relapse or progression following ASCT has occurred in 42 younger patients (58%). The median PFS in this patient group is 21 months from ASCT (Figure 1).

Fifteen elderly patients (68%) are alive with a median follow-up of 21 months (1–40+). Seven elderly patients (32%) have died as of September 2005. Six patients died due to myeloma and one patient from a ruptured abdominal aortic aneurysm. The actuarial median overall



**Figure 1** Progression-free survival (PFS) from the date of transplantation in 92 myeloma patients receiving MEL200 with stem cell support. Solid line: patients <65 years; dotted line: patients ≥65 years. Log-rank:  $P=NS$ .



**Figure 2** Overall survival (OS) from the date of transplantation in 92 myeloma patients receiving MEL200 with stem cell support. Solid line: patients <65 years; dotted line: patients ≥65 years. Log-rank:  $P=NS$ .

survival from the date of ASCT is 57 months for elderly patients (Figure 2). Forty-six younger patients (65%) are alive with a median follow-up of 32 months from ASCT (1–87+). Twenty-four patients (35%) have died to date. Eighteen patients have died due to myeloma. One patient died due to early treatment-related toxicity 1 month after ASCT (*Aspergillus* pneumonia) and another due to myocardial infarction at 10 months. One patient developed Epstein–Barr virus-associated lymphoproliferation and died at 22 months and another died of complications from myelodysplastic syndrome at 84 months. Two patients died as a consequence of later reduced-intensity conditioning allogeneic stem cell transplantation (graft-versus-host disease and infection) 7 and 67 months after ASCT, respectively. The actuarial median OS in younger patients is 66 months from ASCT (Figure 2). No statistical differences were observed in OS between younger and

elderly myeloma patients. By excluding the nine patients who received reduced-intensity conditioned allografts for consolidation or treatment of progression following the autograft, OS did not change (median 66 months from ASCT).

## Discussion

Although HDT with ASCT has become standard care in younger patients with MM, the place of this treatment approach is less clear in patients >65 years of age due to lack of randomized trials. However, several single centre studies<sup>8,9,19</sup> and a registry analysis<sup>10</sup> have shown that this approach is feasible and efficient also in elderly myeloma patients. We compared safety and efficacy of MEL200 with PB support in patients  $\geq$  and <65 years of age treated on the same protocol and conclude that the procedure is safe in selected elderly patients, with an equivalent outcome when compared to younger patients.

Our patient groups were comparable with regard to the major disease characteristics and therapy preceding progenitor cell mobilization. Mobilization with CY plus G-CSF was effective in both age groups, and in more than 95% of patients, an adequate graft was collected after the first mobilization attempt. There were no differences in mobilization efficiency between the younger and older patients. This is in line with previous observations.<sup>20,21</sup> Thus, provided that patients are not heavily pretreated, mobilization and collection of an adequate graft is not a problem in elderly myeloma patients.

Toxicity associated with HDT has been considered an important obstacle for the use of dose-intensive therapy in elderly patients with MM. One approach to reducing the toxicity associated with HD-MEL is to reduce the amount of drug administered. Palumbo *et al.*<sup>12</sup> described a well-tolerated regimen utilizing MEL100 in several cycles supported by blood stem cell infusions. This regimen was associated with an acceptable toxicity profile and promising outcome.

Melphalan 200 mg/m<sup>2</sup> (MEL200) has become a standard high-dose regimen in younger myeloma patients based on a randomized study.<sup>11</sup> In a previous study from Little Rock,<sup>9</sup> MEL200 was regarded as too toxic in patients >70 years of age, with an early treatment-related mortality (TRM) of 16%. Subsequently MEL140 was introduced for this patient population. Sirohi *et al.*<sup>8</sup> reported an early TRM of 17.6% among 17 myeloma patients >65 years of age receiving MEL200 with stem cell support. We have not observed any early treatment-related deaths in elderly patients treated with MEL200. Although the patient group described is relatively small, MEL200 seems to be applicable also in selected myeloma patients  $\geq$ 65 years of age.

We have compared age-dependent toxicity and need for supportive care in our patient cohorts treated with similar protocols. No statistically significant differences were observed in need for supportive care in the length of in-hospital stay, suggesting that there are no differences in terms of resource utilization and costs associated with ASCT between younger and elderly patients.

Our analysis suggests that although MEL200 was also generally well-tolerated in elderly myeloma patients, WHO grade 3–4 toxicity mostly oral mucositis and diarrhea were more common in the elderly patients. On the other hand, other severe organ toxicities were not observed in elderly patients in this study. As the main dose-limiting toxicity of high-dose MEL used with stem cell support is mucositis and diarrhea,<sup>13</sup> there might be a need for studies aiming to prevent these toxicities. Elderly patients undergoing stem cell transplantation with MEL200 might be an appropriate patient group for such studies. In fact, amifostine<sup>22,23</sup> has already been shown to reduce toxicity of HDT in myeloma patients in randomized trials. Palifermin has also shown significant efficacy in preventing the mucosal toxicities associated with TBI-based regimens in patients with non-Hodgkin's lymphoma.<sup>24</sup> There seems to also be a case for studying the potential efficacy of palifermin in elderly myeloma patients receiving MEL200.

Response rates after ASCT were comparable in our study, irrespective of the age. This suggests that age *per se* does not affect the efficacy of MEL200. In addition, no significant differences were observed between the age groups in terms of PFS or OS either. Some previous studies have suggested equal survival rates for elderly patients,<sup>8,10,19,25</sup> whereas others have indicated poorer survival figures for elderly myeloma patients.<sup>26,27</sup> Our study suggests that outcome is comparable when the same treatment intensity is used in elderly patients. Recently, a randomized French study in elderly myeloma patients showed that thalidomide with melphalan-prednisone (MP) was superior to tandem autotransplantation with MEL100.<sup>28</sup> This study raises important questions with regard to optimum first-line treatment in elderly myeloma patients.

Patient selection has a significant impact on the toxicity and outcome of HDT. The proportion of myeloma patients over 65 years of age included on the HDT protocol increased during the study period from 12% in 1998–1999 to 21% in 2002–2003, and to 30% during 2004–2005. By assuming a median age of around 65 years for patients with newly diagnosed myeloma and assuming that at least 80% of patients <65 years are eligible for ASCT, about a quarter of patients with MM over 65 years of age have been included into HDT protocols over the most recent years. Although no specific exclusion criteria were applied to elderly patients during the study period, transplanted patients were generally fit without significant co-morbidities.

To conclude, MEL200 supported by autologous blood stem cell transplantation is a safe and effective treatment in selected myeloma patients  $\geq$ 65 years. Mucosal toxicity seems to be more common in elderly patients but no significant differences exist in the amount of supportive care needed. Age *per se* should not be used as the sole exclusion criterion for this form of treatment but limited data are currently available on the feasibility of this regimen in patients over 70 years of age.

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