



Conditioning with melphalan 200 mg/m² and subsequent ASCT improves progression-free and overall survival in elderly myeloma patients compared to standard of care

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Abstract

Objectives: Despite the effectiveness of newer drugs for the treatment of multiple myeloma (MM), the outcomes are further improved by subsequent autologous stem cell transplantation (ASCT). Data on effectiveness in older patients are limited. We compared outcomes in patients aged 65–75 years depending on whether they were treated with ASCT or not and compared those to outcomes in patients <65 years.

Methods: This was a retrospective, single-center study. We compared progression-free survival (PFS) and overall survival (OS) for all MM patients below and above the age of 65 years treated ± ASCT at the Karolinska University Hospital between 2010 and 2020. PFS and OS were calculated by the Kaplan–Meier method. Variables affecting PFS and OS were evaluated using Cox regression model.

Results: Both PFS and OS were improved in the group 65–75 years treated +ASCT compared to those treated pharmacologically ($p = 0.008$ and $p < 0.001$, respectively). There were no significant differences between patients <65 years and those 65–75 years treated with ASCT.

Conclusion: The findings indicate that even patients >65 years should be evaluated as candidates for ASCT. An individualized approach supported by a frailty/geriatric assessment score could assist clinicians to select the appropriate treatment for each patient.

KEYWORDS

aged, multiple myeloma, progression-free survival, stem cell transplantation

1 | INTRODUCTION

The introduction of several new agents, such as proteasome inhibitors (PI), immunomodulatory drugs (IMiDs), and most recently

monoclonal antibodies (mAbs) as first-line treatment in patients with multiple myeloma (MM) has contributed to a better overall survival (OS).^{1–3} Nevertheless, the conditioning regime with high-dose melphalan (Mel, 200 mg/m²) followed by autologous stem cell transplantation (ASCT) is the established standard treatment for MM patients younger than 65 years of age and can improve both

Gabriel Afram and Roza Chaireti contributed equally to this study.

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progression-free survival (PFS) and OS radically, at least in some subgroups.⁴ However, the role of ASCT in the treatment of elderly patients is debatable, especially since the introduction of PI, IMiDs, and mABs as first-line treatments.

In MM, Mel is used almost exclusively as conditioning prior to ASCT. Typically, Mel is administered at a fixed dose of 200 mg/m² (Mel200) except for patients with renal impairment for whom a dose reduction (140 mg/m²) is recommended. The toxicity of Mel in patients older than 65 years might pose a hurdle and is mostly attributed to the anticipated reduction in organ function as well as altered drug metabolism and excretion. Badros et al.⁵ described a small cohort of elderly patients who received Mel at a dose of either 200 mg/m² or 140 mg/m² prior to ASCT. The lower dose was less toxic, and its efficacy was comparable to that of the full dose. Palumbo et al.⁶ conducted a clinical trial where two to three courses of Mel at a dose of 100 mg/m² were given prior to ASCT with beneficial outcome in elderly MM patients compared to standard treatment.

Thus, it has been shown that conditioning with Mel followed by ASCT prolongs PFS and improves OS, both in young and in fit elderly patients. To explore the potential benefit of Mel200 and ASCT in elderly (>65 years) MM patients, we performed a retrospective study, which evaluated PFS and OS in 190 patients treated with ASCT at our center during 2010–2020. We then compared the outcomes to the non-ASCT-treated patients in the same age group as well as to the ASCT-treated patients aged <65 years during the same time period.

2 | MATERIAL AND METHODS

2.1 | Study population

The patient cohort consisted of 1077 newly diagnosed multiple myeloma (NDMM) patients treated at the Department of Hematology, Karolinska University Hospital, Stockholm, Sweden between January 2010 and April 2020. The patients were divided into three groups: (i) patients aged <65 years ($n = 522$) treated with Mel200 and ASCT (+ASCT); (ii) patients aged 65–75 years ($n = 190$) treated with Mel200 and ASCT (+ASCT); and (iii) patients aged 65–75 years ($n = 365$) not treated with ASCT (–ASCT). Clinical data were collected from the hospital's electronic medical records. The study was approved by the Ethics committee in Stockholm.

Sub-analyses of patients aged 65–70 years \pm ASCT were also performed when possible.

Data for age, sex, and type of MM, as well as laboratory measurements, were collected as earlier described.^{7–10}

2.2 | Multiple myeloma treatment

During the study period, PIs and IMiDs were introduced as 1st line treatment for MM and all patients received the same treatment according to the guidelines which were current at that time, regardless of whether they were also treated with ASCT.

Between 2010 and 2016, all patients received bortezomib, cyclophosphamide, and dexamethasone (VCD) as induction treatment,⁹ whereas between 2017 and 2020, bortezomib, lenalidomide, and dexamethasone (VRD) were given as induction.¹¹ VCD was given in 3-week cycles with bortezomib 1.3 mg/m² subcutaneously (sc) on Days 1, 4, 8, and 11, cyclophosphamide 1000 mg/m² intravenously (iv) on Day 1 and dexamethasone 20 mg per day orally on Days 1, 2, 4, 5, 8, 9, 11, and 12. The patients treated with VRD received bortezomib and dexamethasone as in the VCD regimen (see above), whereas lenalidomide was given at a dose of 15–25 mg on Days 1–14 (median 4 cycles). The dose of lenalidomide was adjusted depending on kidney function.

For patients between 65 and 75 years of age, both VCD and VRD were administered in 5-week cycles. Bortezomib was given once weekly for 4 weeks and dexamethasone (20 mg) was administered on the same day and the day after bortezomib, in both VCD and VRD regimens. Cyclophosphamide was given at the first day of each VCD cycle, and lenalidomide (25 mg) was given on Days 1–21 of the 35-day cycles (5 weeks) or every other day continuously during the VRD cycles. The standard of care is 9 cycles.

After the induction treatment, cyclophosphamide at a dose of 2 g/m² and filgrastim were used for stem cell mobilization. High-dose treatment (HDT) with melphalan 200 mg/m² was administered within 2–4 weeks after stem cell harvest, as earlier described,⁸ followed by ASCT. In case the patients started maintenance therapy, they were censored at that date.

2.3 | Statistical methods and data management

PFS and OS were calculated using the Kaplan–Meier method and the comparison between groups was made using the log-rank test. PFS and OS were calculated from data extracted from digital medical records and were defined as the primary end points. The variables predicting PFS and OS were evaluated using Cox regression models to estimate hazard ratios (HR). First, univariate risk factors were analyzed, and only significant risk factors were included in the subsequent multivariate model. All p values were calculated by two-tailed tests, and a p value of <0.05 was considered significant. The analyses were performed using Statistica (StatSoft, 2018) and SPSS (IBM Corp., 2018).

3 | RESULTS

3.1 | Patient characteristics

For the subgroup aged 65–75 years, patients treated with ASCT were slightly younger than those who did not receive ASCT (median age 68 vs. 71 years, $p < 0.001$). In the same group, 65% of the +ASCT and 54% of the –ASCT patients were male. FISH data were available at diagnosis for 183 patients aged 65–75 years, of which 80 patients (44%) were stratified as having high risk (HR) cytogenetic aberrations and 103 (56%) as having standard risk (SR) aberrations. Of the patients with HR, 46% were treated with ASCT and 41% were not. In

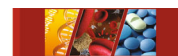


TABLE 1 Patient characteristics at diagnosis for patients treated with: (a) +ASCT at ≤ 65 years (y) of age, (b) +ASCT > 65 years (y) of age, and (c) –ASCT, 65–75 years (y) of age

	+ASCT ≤ 65 y n = 522 (a)	+ASCT > 65 y n = 190 (b)	–ASCT 65–75 y n = 365 (c)	p value (a vs. b)	p value (b vs. c)
Age	56 (38–75)	68 (65–75)	71 (65–75)	<0.001	<0.001
Sex, male (%)	59%	65%	54%	0.695	0.010
Bone lesion (%)	93%	91%	82%	0.709	0.137
S-albumin (g/L)	33 (11–50)	33 (16–45)	32 (13–47)	0.361	0.145
S-calcium (mmol/L)	86 (37–1404)	89 (52–1751)	77 (53–168)	0.110	0.005
Beta-2-microglobulin (mg/L)	4.9 (1.2–49.0)	5.1 (1.0–32.0)	5.6 (1.0–66.0)	0.817	0.643
S-creatinine (μ mol/L)	86 (37–1404)	89 (52–1751)	77 (53–168)	0.110	0.005
del17p, t(4;14), t(14;16), and/or add1q (%)	46%	46%	41%	0.977	0.535

Note: All values are expressed as median (range) unless otherwise specified. Bold indicate significant values ($p < 0.05$).

TABLE 2 Patient characteristics at diagnosis in patients aged 65–70 years (y) treated with and without ASCT

	+ASCT n = 158	–ASCT n = 234	p
Age	67	67	0.502
Sex, male (%)	64%	56%	0.136
S-albumin (g/L)	32 (15–44)	30 (15–42)	0.017
Bone lesion (%)	93%	85%	0.341
S-calcium (mmol/L)	2.42 (2.03–3.75)	2.42 (2.06–4.05)	0.911
Beta-2-microglobulin (mg/L)	5.4 (1.2–35)	5.7 (1.0–66.0)	0.851
S-creatinine (μ mol/L)	84 (52–1407)	73 (39–168)	0.033
Del17p, t(4;14), t(14;16), and/or add1q (%)	45%	36%	0.371

Note: All values are expressed as median (range) unless otherwise specified. Bold indicate significant values ($p < 0.05$).

the group of patients aged 65–75 years ($n = 556$), FISH data were evaluated in 183 (33%). Of those, 80 patients presented with add1q21, del17p21, t(4; 14), and/or t(14;16) and were defined as HR MM patients.

Of the 190 patients > 65 years treated with Mel200 + ASCT, only 32 (17%) were above the age of 70 years at diagnosis. Of the patients not treated with ASCT, 131 (36%) were above the age of 70 years (Tables 1 and 2).

The patients < 65 years treated with VCD during 2010–2016 received a median of 4^{4–8} cycles. The patients aged 65–75 years received a median of 6^{2–12} treatment cycles for both VCD and VRD regimes.

3.2 | PFS and OS in all patient groups (below and above 65 years of age)

The median PFS of +ASCT patients aged < 65 years was 3.1 years. The median PFS in +ASCT patients aged 65–75 was 2.5. The PFS for –ASCT patients aged 65–75 years was 2.1 years (Figure 1A).

The median OS was not reached for +ASCT patients regardless of age (66% at 6 years for < 65 years and 60% at 6 years for 65–75 years). However, –ASCT patients aged 65–75 had a median OS of 6 years (Figure 1B). No statistical differences were found in the median PFS or OS in patients undergoing ASCT regardless of age ($p = 0.122$ and 0.733 for patients aged < 65 or 65–75 years, respectively).

In the group treated with Mel200, 41 patients had HR cytogenetics. In the group not treated with Mel200, 39 patients were stratified as HR. No significant differences in the median PFS or OS in the two groups were noted.

3.3 | PFS and OS in patients aged 65–75 years

In the age interval 65–75 years ($n = 555$), 190 patients were treated with Mel200 + ASCT (34%). The group treated with Mel200 had improved OS and PFS ($p = 0.008$ and $p < 0.001$, respectively) compared to those –ASCT.

Among 253 patients aged 70–75 years, only 31 (12%) were treated with Mel200 + ASCT. No differences in PFS or OS were found,

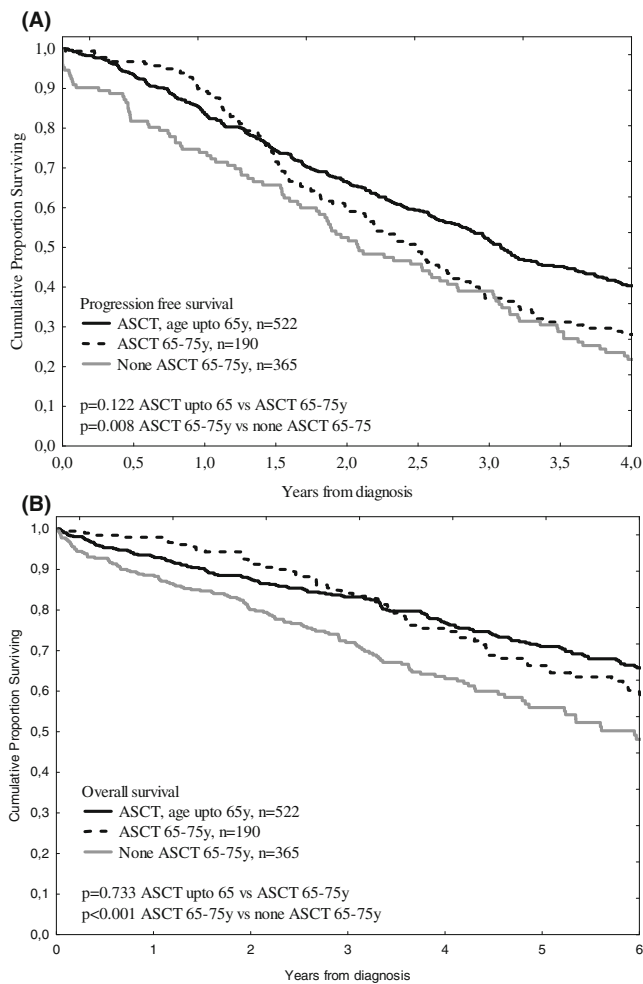


FIGURE 1 Progression-free survival (A) and overall survival (B) for all patients aged up to 65 years treated with ASCT, for patients aged 65–75 years treated with ASCT, and for patients aged 65–75 years not treated with ASCT

with the median PFS being 1.9 years for both groups ($p = 0.272$), and the median OS 5.7 and 6 years for those treated and not treated with Mel200, respectively ($p = 0.102$). Due to the uneven size of the groups (+ or –ASCT), no additional analyses were performed.

3.4 | PFS and OS in patients 65–70 years

During the period 2010–2020, 392 patients aged 65–70 years were diagnosed with MM at our center. Of those, 158 patients (40%) were treated with Mel200 + ASCT. The median PFS at 2 years was 62% and 51%, respectively (\pm ASCT), but in both groups, it was reached at 2.5 years. However, OS was not reached, being 65% at 6 years when the patients were treated with Mel200 and 5.3 years for those not treated with Mel200, $p = 0.043$ (Figure 2). The univariate analysis revealed a significance difference in S-albumin (30 g/L vs. 32 g/L, $p = 0.017$) and S-creatinine (84 μ mol/L vs. 73 μ mol/L, $p = 0.033$) in the group treated versus the group not treated with Mel200 (Table 2).

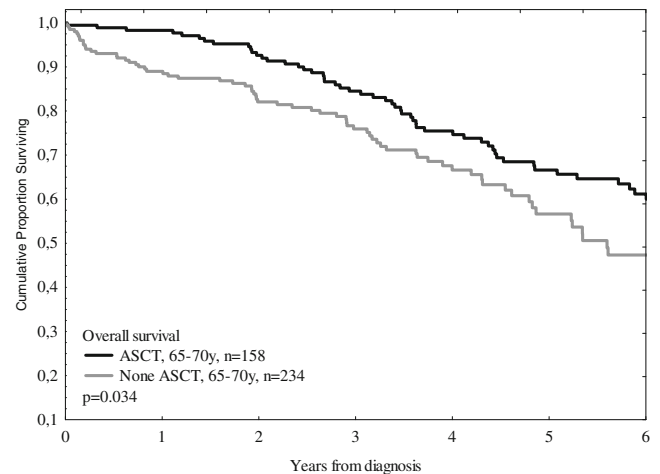


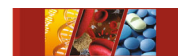
FIGURE 2 Overall survival for patients 65–70 years treated and not treated with ASCT

4 | DISCUSSION

The choice of first-line treatment is a major factor for ensuring good prognosis in patients with MM.⁷ Although age has been one of the central criteria in choosing which patients are eligible for ASCT, there have been reports supporting the use of this regime even in older (>65 years) patients citing efficacy without significantly higher toxicity.^{11–13}

Our results demonstrate that the median PFS and OS were improved in patients with MM aged >65 years who were treated +ASCT compared to –ASCT patients ($p = 0.008$ and $p < 0.001$, respectively). Even in the subgroup aged 65–70 years, where 40% of the patients were treated with ASCT, the improvement of the PFS was modest and more patients reached the median OS of >6 years in the Mel200 arm. Although the results suggest that ASCT did not improve survival in patients aged 70–75 years, far less patients were treated with ASCT in this age group and the subgroups were thusly unequal in size, making it difficult to draw robust conclusions. There could be additional bias when choosing which patients will receive ASCT in this group, considering the presence of co-morbidities, patient preferences, and possible reluctance to use ASCT in patients >70 years. We did not examine the role of the aforementioned factors, nor their effect on physician recommendations, and can thusly not state with certainty whether survival would be unchanged even without ASCT.

A recent Australian two-center study presenting real-world data on the efficacy of ASCT in elderly patients (>65 years) showed that median PFS and OS were higher in the group younger than 65 years, but both endpoints were comparable in the groups 60–64, 65–69 and above 70 years of age.¹³ Their cohorts were similar to ours in that there were no significant differences in the baseline characteristics between the older and younger patients. Additionally, even in the Australian cohort, most of the elderly patients received full-dose Mel as conditioning, without significant increase in the transplantation-related mortality (TRM). This confirms our results on the favorable



effect of ASCT in older patients, even in cohorts treated at different centers.

In Phase 3, randomized, case-control study, the MAIA investigators showed that addition of daratumumab to lenalidomide plus dexamethasone when treating patients ineligible for ASCT, increases PFS and leads to better treatment response compared to the patients not treated with daratumumab.¹⁴ There were more cases of pneumonia and neutropenia in the patients in the daratumumab arm¹⁴ in the initial report. The more resect frailty report using age, Charlson comorbidity index, and baseline Eastern Cooperative Oncology Group, confirmed that the risk for 3/4 treatment-emergent adverse events was higher in the frail group, but could be managed.¹⁵ The higher toxicity indicates that there is room for improvement when evaluating the frailty status of elderly patients. We did not use a frailty score other than the Karnofsky score. However, since there were a lot of missing data, we did not include the results in our analysis. A more thorough risk stratification in the elderly population could increase the number of patients who are candidates for ASCT.

In a previous trial on a comparable cohort, only four deaths were reported when using 200 mg/m² melphalan.⁶ In the current study, only one death occurred within 100 days post-ASCT. This could be an indication of the low toxicity of this treatment. However, since we did not study other markers of toxicity, we cannot draw a stronger conclusion. In contrast with the study by Auner et al.,¹⁶ we did not evaluate the disease status at transplantation. They did confirm low toxicity among patients treated with Mel200, by comparing to corresponding available outcomes in those treated with Mel140. In our cohort, all patients, regardless of disease status, were pretreated with Mel200, since this is the standard treatment with optimal conditioning effect. The number of patients treated with Mel140 at our center is too low and does not allow for a comparison.

In a study by Straka et al.¹⁷ patients were treated with different dosages of melphalan (ranging from 100/140 mg/m² to totally 400 mg/m²) and improved PFS was shown among patients with higher cumulative doses, but administration of Mel200 was superior to Mel100/140 only in patients who were not consolidated with bortezomib. The results from the CIBMTR database¹⁸ showed worse outcomes among patients older than 70 years of age who were treated with Mel140 compared to Mel200. In our cohort, all patients were given the same melphalan dose (Mel200) and we showed superior PFS and OS associated with this treatment. Toxicity was not evaluated further than by the treatment was overall well tolerated; however, Mel140 could be an alternative for very frail patients with good disease status prior to transplantation.

In 2015, a report from the International Myeloma Working Group proposed a geriatric assessment score (frailty score) with markers from three assessment tools concerning co-morbidities and self-sufficiency in order to determine the risk for treatment-associated mortality and toxicity.¹⁹ This score could predict survival and risk for toxicity in elderly patients (median age 74 years).¹⁹ However, the score was developed based on data from patients participating in clinical trials, where the frailest patients were excluded. Validation of such scores in real-world patients, such as those in our study, could

strengthen the predictive value and even contribute with new markers.

One of the main strengths of this study is the large cohort ($n = 1077$) which allows us to draw reliable conclusions. Additionally, since this is a single-center study, all the patients were treated by the same protocol (even if this changed during the course of the study) and also received the same standard of care concerning handling adverse effects and toxicity. One weakness of the study is its retrospective character; the quality and completeness of the data gathered from medical records is dependent on the meticulousness of the medical practitioner who wrote those. However, the endpoints of the study, namely PFS and OS, can be calculated objectively and are not subject to different readings. Additionally, this was not a case-control matched study, and the results must be interpreted accordingly. On the other hand, the data reflects the reality and challenges of treating patients with multiple myeloma in a rapidly aging global population. No toxicity data was gathered, but 100-day mortality post-ASCT was very low. Very frail patients were not offered the option of ASCT, and the selection of those considered eligible for ASCT depended heavily on the physician's judgment. We did not use additional, pre-defined disease characteristics and that could be a source of bias.

The field of transplantation among elderly patients still lags behind and awaits randomized controlled trials to synthesize solid guidelines.²⁰ Considering the fact that the median age at diagnosis is 70 years, it is imperative to further investigate the safety of therapies proven to be highly efficient in younger populations. Our study contributes to this field, indicating that, at least up to the age of 75, ASCT with prior Mel conditioning is well tolerated and prolongs survival.

In 2018, the European Myeloma Network suggested using chronological, rather than biological age, along with performance status, to decide which patients are eligible for ASCT.²¹ Considering both our results and those from other related studies,^{11,13,22} this would appear to be both logical and feasible. An individualized risk scoring according to the principles of precision medicine would benefit patients and support the clinicians in their decision-making. Our conclusion is that a fit MM patient above the age of 65 years should be considered and evaluated as a candidate for ASCT.

4.1 | Significance statement

This study provides evidence that elderly (older than 65 years) patients with multiple myeloma can benefit from stem cell transplantation without significant toxicity. The current recommendations indicate that those patients should not be routinely considered as candidates for this treatment since there is a high risk for complications. Our results are important since stem cell transplantation increases the chance of longer and disease-free survival and can thus help those patients lead a longer and healthier life. Our study provides results that can help physicians who treat patients with multiple myeloma choose the therapeutic approach with the best outcomes.



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CONFLICTS OF INTEREST

Gabriel Afram is employed by Pfizer AB. Hareth Nahi is employed by Genmab. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available upon request from the authors.

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