Autologous stem cell transplantation in elderly patients with multiple myeloma: evaluation of its safety and efficacy.

Original Article

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ABSTRACT

Administering high-dose chemotherapy (HDCT) with melphalan to elderly myeloma patients represents a challenge with respect to achieving therapeutic efficacy whilst avoiding significant toxicity. We analyzed safety and efficacy of HDCT in 61 elderly myeloma patients older than 65 years, including 12 patients ≥70 years, and compared them to 237 MM patients below 65 years treated in the same period. MM patients older than 70 years had a longer duration of hospitalization (26 vs. 20 days; *P*=.0001) and a longer time until platelet recovery >20 G/L (19 vs. 15 days; *P*=.0398). However, we observed no differences in the time until neutrophil recovery, infection rate, and treatment related mortality until 100 days after ASCT. Furthermore, higher age was not associated with inferior progression-free and overall survival at 1 and 2 years after ASCT. Our data suggest that HDCT with ASCT is feasible, safe and effective in MM patients older than 65 years.

INTRODUCTION

Symptomatic multiple myeloma (MM) is a malignant plasma cell disease characterized by the presence of a specific monoclonal immunoglobulin and related organ damages including hypercalcemia, renal insufficiency, anemia, or lytic bone lesions (CRAB) [1,2]. Most symptomatic MM patients are elderly, defined as being older than 65 years of age, with the incidence of MM increasing along the aging of the general population and its increasing life expectancy.

Since the late 1990s, high-dose melphalan treatment (200mg/m2) followed by autologous stem cell transplantation (ASCT) has been regarded as a standard procedure for younger MM patients in the absence of relevant comorbidities [3-5]. In the first decade of the 21st century, bortezomib-based regimens have become standard induction therapy preceding ASCT in transplant-eligible patients and have additionally contributed to improved survival for younger MM patients [6-10]. However, the significant improvement in overall survival has mainly been observed in younger MM patients [11-17], whereas advances for elderly MM patients have been less significant [11,14,16,18].

MM patients aged older than 65 years are usually considered as ineligible for high-dose melphalan therapy (200mg/m2) followed by ASCT mainly because of impairment in organ functions and reduced drug metabolisms. Consequently, clinical trials involving ASCT have mostly been restricted to patients younger than 65 years with few exceptions. The toxicity of 200mg/m2 high-dose melphalan was investigated in 25 elderly patients aged 70 years or older [19] resulting in four (16%) transplant-related deaths (TRM), but after reducing the dose to 140mg/m2 the TRM could be reduced to 2% while maintaining the efficacy. Of crucial importance was a

subsequent trial with 2-3 courses of ASCT with 100mg/m2 of melphalan in 71 patients aged up to 75 years [20]. When compared with matched-pair patients treated with melphalan and prednison (MP), the efficacy of ASCT was significantly superior to MP in terms of complete response (CR) rate, event-free survival (EFS) and OS, without transplant-related deaths. Based on these reports, elderly patients with MM in otherwise fit medical condition have been considered to be eligible for ASCT irrespective of the chronological age in many institutions [21,22]. Accordingly, several single institution studies have reported their experience of ASCT in elderly patients [23-30]. As conditioning regimen before ASCT, reduced dosing of melphalan (100–140mg/m2) has been predominantly used in elderly patients, with no significant difference in transplant-related mortality and morbidity between elderly and younger patients. Recently, the transplant-related mortality in MM patients has decreased to 2-4%, probably due to the improvement of supportive therapies [31]. As a consequence, reduced-intensity ASCT is considered to be a safe and effective therapeutic modality even in MM patients aged 65-75 years in a good performance status without relevant comorbidities. Accordingly, physicians increasingly tend to raise the upper age limit, and a substantial number of elderly MM patients is offered ASCT in clinical routine nowadays.

In order to further evaluate the safety and efficacy of ASCT in this cohort of patients, we performed a retrospective analysis of data obtained from elderly MM patients aged older than 65 years at our center. We compared these results with data obtained from MM patients younger than 66 years of age treated in the same period to assess the toxicity and the survival benefit of HDCT with ASCT in elderly MM patients.

MATERIAL AND METHODS

Patients: Patients with MM consecutively seen at the University Hospital of Bern, Switzerland from January 2009 to May 2015 who received at least one HDCT with ASCT were studied. All patients had given written informed consent, and this study was approved by the local ethics committee of Bern, Switzerland (decision number #149-14). The patients were stratified into three groups according to their age at ASCT. Group 1 comprised MM patients aged 18-65 years, group 2 involved MM patients aged 66-69 years, and MM patients in group 3 were ≥70 years.

Treatment

According to local standards, non-myelosuppressive chemotherapy with vinorelbine or gemcitabine, but not cyclophosphamide, together with G-CSF was used for mobilization of autologous stem and progenitor cells [32-34]. At least $3x10^6$ CD34+ cells/kg body weight (b.w.) were collected per planned stem cell transplantation. Patients above 70 years received a reduced dose of melphalan (140mg/m2), whereas patients ≤70 years were administered full dose melphalan (200mg/m2); the dose of melphalan was reduced to 140 mg/m2 for patients with reduced renal function with a creatinine-clearance between 40-50ml/min, and to 100mg/m2 for patients with a creatinine-clearance below 40ml/min. All patients received weight adapted G-CSF starting at day 6 after ASCT until neutrophils exceeded 0.5 G/L for three consecutive days. Patients routinely had antiviral (acyclovir 500mg twice daily) and antifungal prophylaxis (fluconazole 400mg once weekly and sulfamethoxazol/trimethoprim 800/160mg three times per week).

Definitions

Objectives of the study with regards to safety were duration of hospitalization, time until neutrophil and platelet recovery, rate of febrile episodes, and mortality until 100 days after ASCT, as well as the occurrence of unexpected toxicities during and after hospitalization for ASCT until 100 days after ASCT. Neutropenia was defined as neutrophil counts <0.5 G/l, and thrombocytopenia as platelet counts <20 G/l. The mortality until day 100 was defined as death from any cause within 100 days after ASCT, and TRM was defined as transplant-related death due to toxicity or infectious complications following ASCT.

OS was defined as the time from ASCT until death from any cause or last follow-up. PFS was defined as the time from ASCT until first relapse/progression, death or last follow-up, whichever occurred first. Complete remission (CR) was defined as a negative immunofixation in serum and urine, absence of plasmocytoma and less than 5% plasma cells in the bone marrow. A reduction of ≥50% of serum M-protein was considered a partial response (PR). Progression (PD) was defined as an increase of at least 25% in measurable monoclonal immunoglobulin in serum or urine or an increase of ≥25% in urinary light chains. If CR lasted less than 3 months, it was defined as progression (PD).

Statistical Analysis

Survival curves were calculated using the method of Kaplan and Meier and compared using the log-rank test. Differences in the mean values of continuous variables were tested using the t-test. All statistical analyses and graphs were performed using graph pad prism program 7.00 (Trial Version) or Microsoft Excel (Microsoft Office 2016). P-values <0.05 were considered statistically significant.

RESULTS

We identified a cohort of 298 patients with symptomatic multiple myeloma (MM) who received at least one high-dose chemotherapy (HDCT) with melphalan with autologous stem cell transplantation (ASCT) between January 2009 and May 2015 at the University Hospital Bern, Switzerland. The patients were divided into three age groups: Group 1 comprised MM patients aged 18-65 years, group 2 involved MM patients aged 66-69 years, and MM patients in group 3 were ≥70 years. The patient characteristics at diagnosis are summarized in **Table I**. We observed that elderly MM patients (group 2) had more frequently advanced disease (ISS stage III) than younger MM patients in group 1 (59% vs. 39%; *P*=.0073), respectively. The **Supplemental Table I** depicts the mobilization and high dose chemotherapy regimens used in this study.

Table II depicts the details on mobilization and collection of autologous stem and progenitor cells. All MM patients were mobilized with a single dose of non-myelosuppressive chemotherapy using 35mg/m2 of vinorelbine or 1250mg/m2 of gemcitabine (but not cyclophosphamide) together with G-CSF [32-34], with a collection goal of at least $3x10^6$ CD34+ cells/kg body weight (b.w.) per planned stem cell transplantation. Apheresis was initiated based on pre-collection peripheral CD34+ cell counts, and a minimum of 15 peripheral CD34+ cells/μl was necessary to trigger the collection procedure. The minimal number of collected CD34+ cells to proceed to transplantation was $2x10^6$/kg b.w.

254 MM patients (85%) achieved the pre-defined collection goal in a single apheresis day procedure, whereas 44 patients (15%) needed two days. Whereas we observed no differences between the three age groups in the number of apheresis days needed (two days of apheresis in 14%, 20%, and 17% in groups 1, 2 and 3, respectively, *P* =.455), we found that elderly patients mobilized significantly less circulating peripheral CD34+ cells at the day of stem cell collection ($110x10^6$/l, $77x10^6$/l and $50x10^6$/l in groups 1, 2 and 3, respectively, *P* =.0097). Also, the percentage of circulating CD34+ cells per peripheral leukocytes at the day of stem cell collection was lower in elderly MM patients (0.5%, 0.29%, and 0.26% in groups 1, 2 and 3, respectively, *P* =.2914). Due to a longer duration of stem cell collection in elderly patients (details not shown), the total number of collected CD34+ cells was comparable in all three age groups. Accordingly, the total number of re-transfused autologous stem cells was similar in all three age groups (Table II).

All MM patients in this cohort received melphalan conditioning as planned: Patients above 70 years were given a reduced dose of melphalan 140mg/m2, whereas melphalan 200mg/m2 was administered in patients younger than 70 years. The melphalan dose was reduced to 140 mg/m2 for patients with reduced renal function with a creatinine-clearance between 40-50ml/min, and to 100mg/m2 for patients with a creatinine-clearance of below 40ml/min.

We observed that age ≥70 years (group 3) was associated with prolonged hospitalization for HDCT with ASCT compared to the age groups 1 and 2 (26 days in group 3 vs. 19 and 20 days in groups 1 and 2; *P* =.0.001). We also found differences for the time needed until hematologic recovery (**Table III**). Age ≥70 years (group 3) was associated with a prolonged duration until recovery of platelets above 20G/L (20 days in group 3 vs. 13 days in groups 1 and 2; *P* =.007). In contrast, no differences

were seen between the three age groups in the duration of neutropenia (12, 11 and 11 days in groups 1, 2 and 3, *P* = .0751).

A total of 44 patients have died since ASCT (15%). Four (1%) patients – all aged below 66 years - died within 100 days after ASCT, and all four (1%) deaths were due to transplant-related causes (TRM) comprising one patient dying because of septic shock and three patients dying because of respiratory tract infections with respiratory failure (**Table III**). TRM was not different among the three age cohorts (2% in group 1 and 0% in groups 2 and 3; *P* =.5935).

The number of febrile episodes and the number of febrile episodes with identification of a causing germ was similar between the three age groups, both during hospitalization as well as after discharge until 100 days after ASCT. Similarly, no differences were observed for the rate of severe complications and/or additional hospitalizations after discharge from HDCT/ASCT treatment between the three cohorts (13%, 22%, and 17%; *P*=.2016).

Before ASCT, the rate of patients in CR after induction treatment was comparable between the three age groups (**Supplemental Table II**). Similarly, we observed no differences in the rate of achieved complete remissions (CR1) 100 days after ASCT (47%, 45%, and 58% in groups 1, 2 and 3; *P* =.7018). After a mean follow-up of 21 months after ASCT, 114 myeloma patients (38%) in our cohort had a relapse, and the relapse rate was not higher in older patients (42%, 20%, and 33%; *P*=.0151), and the median duration until first relapse was similar in all three age groups (22, 18 and 8 months in group 1,2 and 3; *P*=.121). We observed no differences in the PFS between the three age groups (**Figure 1**).

Finally, 44 deaths (15%) were reported in our cohort, with age above 65 years not being associated with increased death rate (18%, 2%, and 0% in group 1, 2 and 3; *P*=.0052). The OS was not inferior for elderly myeloma patients compared to patients below 66 years (**Figure 1** and **Supplemental Table II**). As expected, the failure to achieve CR within 100 days after ASCT was associated with a less favorable PFS and OS (*P*=.0001) (**Supplemental Figure 1A and 1B**). For patients achieving a CR after ASCT, PFS and OS for patients above 65 years were comparable to younger myeloma patients (**Supplemental Figure 1C and 1D**). These data suggest that elderly fit myeloma patients experience similar survival benefits from HDCT with ASCT as myeloma patients below 66 years.

DISCUSSION

Few studies are available which incorporated consolidation with ASCT into the treatment algorithm for elderly symptomatic myeloma patients in the era of novel agents. Two phase II trials have consolidated the induction treatment - with four cycles of bortezomib, pegylated liposomal doxorubicin and dexamethasone - with tandem ASCT (each 100mg/m2 of melphalan), followed by consolidation therapy with four cycles of lenalidomide and prednisone, and a maintenance therapy with lenalidomide alone in patients aged 65-75 years [35,36]. The median PFS was 48 months, and the 5-year overall survival (OS) was 63%; notably, patients achieving a CR had a 5-year OS of 83%. The treatment-related mortality associated with ASCT in these two trials was significantly higher in MM patients ≥70 years (19%) compared with that of MM patients (4%) less than 70 years (*P*= 0.024); thus, one might conclude that a sequential approach including reduced-intensity ASCT may benefit patients younger than 70 years of age with good performance status and without comorbidities [37-39]. In line with these reports we found in our retrospective single-center cohort not a single treatment-related death during the 100 days after ASCT in 71 MM patients aged between 66 and 69 years. However, we also observed no treatment-related death in a (small) cohort of 20 myeloma patients aged ≥70 years at ASCT. Our data therefore point to the possibility that age adapted high-dose melphalan with ASCT can be safely applied to consolidate induction treatment with novel agents in elderly fit myeloma patients, including myeloma patients above the age of 70 years.

Importantly, we followed a strategy of applying 200mg/m2 melphalan before ASCT in myeloma patients below 70 years, and we reduced melphalan to 140mg/m2 for

patients ≥70 years. In addition, dose reductions were performed for patients with reduced renal function. The transplant-related mortality (TRM) for melphalan 200 mg/m2 in elderly myeloma patients was reported to be up to 19% (17), while that for 100 mg/m2 of melphalan was 0% (19) and 2% for 140 mg/m2 melphalan (20). Our single-center results with a TRM of 0% in 71 myeloma patients aged 66-69 years treated with 200mg/m2 melphalan challenge the need for dose reductions in myeloma patients in this age cohort considered to be fit for high-dose consolidation. In addition, we did not observe differences in the duration of hospitalization, hematologic recovery, number of febrile episodes or of re-hospitalizations in myeloma patients aged 66-69 years compared to patients below 66 years. Therefore, our data suggest that 200mg/m2 melphalan can be safely applied by an experienced transplant team to myeloma patients between 66-69 years within an experienced transplant team.

We applied a reduced dose of 140mg/m2 melphalan to myeloma patients ≥70 years in this study. We observed few, but notable differences compared to 200mg/m2 melphalan in patients below 70 years. The duration of hospitalization was significantly longer in patients ≥70 years (26 vs. 20 days), and the time until platelet (but not neutrophil) recovery above 20 G/L was longer (19 vs. 15 days). Since we did not observe more admissions to the intensive care unit, febrile episodes, or bleeding events, we concluded that the prolonged hospitalization of patients ≥70 years was related to a generally slower recovery from the deterioration of the general condition associated with high-dose chemotherapy.

We observed similar rates of complete remission 100 days after ASCT in patients below 66 years and patients ≥66 years. Also, the progression-free survival and the overall survival was not different between the three age groups in this study. Thus,

these results suggest that elderly myeloma patients may equally benefit from consolidation treatment with HDCT and ASCT as younger myeloma patients in the era of novel agents. However, the obvious limitations of this study need to be stated including the retrospective, non-randomized, single-center design and the limited number of patients in the two elderly myeloma subgroups, as well as the limited follow-up.

CONCLUSION

Our data suggest that consolidation with HDCT and ASCT is feasible, safe and effective in myeloma patients older than 65 years. Age above 65 years, but also age above 70 years should not *per se* exclude patients from treatment with HDCT and ASCT. Therefore, the consolidation with HDCT and ASCT should be considered in elderly fit myeloma patients based on performance status and presence of complications and/or comorbidities, but not on chronological age alone. The sequential approach of MM treatment including ASCT can be challenging, but represents a feasible approach to further improve the outcome of elderly patients with multiple myeloma.

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FIGURE LEGEND

Figure 1: Depicted are Kaplan-Meier survival curves for the entire cohort of all 298 multiple myeloma patients for (**A)** progression free survival and (**B)** overall survival, as well as according to the three age groups for (**C)** progression free survival and (**D)** overall survival.

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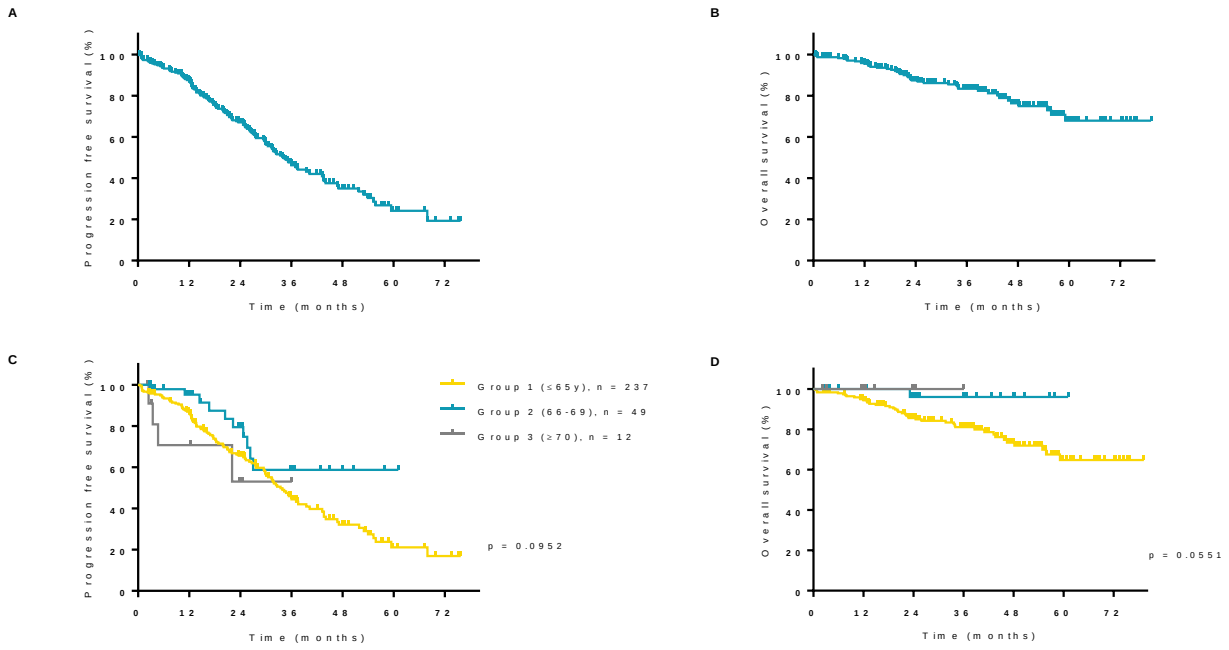
Figure 1


A
Progression free survival (%)
Time (months)
B
Overall survival (%)
Time (months)
C
Progression free survival (%)
Group 1 (≤65y), n = 237
Group 2 (66-69), n = 49
Group 3 (≥70), n = 12
p = 0.0952
Time (months)
D
Overall survival (%)
p = 0.0551
Time (months)