Melphalan dose intensity for autologous stem cell transplantation in multiple myeloma

High-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) remains the standard of care upfront treatment for transplant-eligible multiple myeloma (MM) patients.[1,2] High-dose melphalan 200 mg/m^2 (Mel200) is the standard preparative regimen for MM.[1] Over the past two decades, several prospective clinical trials compared Mel200 to more intense preparative regimens in an attempt to improve efficacy.[3] Generally, none of these regimens showed an overall survival (OS) advantage over Mel200. However, some reported superior progression-free survival (PFS),[4] albeit with higher rates of regimen-related toxicity. Furthermore, older and frail patients are not candidates for more intense regimens.

Reduced-dose melphalan is frequently used as an alternative for older patients and those considered unfit for Mel200 because of frailty or medical comorbidities. Melphalan 100 mg/m^2 (Mel100) was shown to be less effective compared to Mel200, albeit better tolerated.[5,6] An intermediate dose of melphalan 140 mg/m^2 (Mel140) has been widely used in older patients and those with significant comorbidities. Several groups reported feasibility of Mel140, particularly for older patients and those with renal impairment,[7,8] however with conflicting outcomes when compared to Mel200.[9-11] A recent report by the European Society for Blood and Marrow Transplantation (EBMT) showed similar outcomes between Mel140 and Mel200, except for a subset of patients with suboptimal responses to pretransplant induction therapy.[12] In this study, we compared the safety and efficacy of Mel140 *versus* Mel200 in a recent cohort of MM patients who received an ASCT at our institution.

We included all consecutive adult patients, who were 18 years or older, with newly diagnosed MM who underwent upfront ASCT consolidation and received single agent HDC of Mel140 or Mel200. Primary endpoints were PFS and OS, computed from date of transplant. Secondary endpoints included cumulative incidence of relapse (CIR), non-relapse mortality (NRM), and toxicities. OS and PFS estimates for each melphalan group were obtained from Cox regression models, adjusting for the selected variables. We identified 911 eligible patients between January 2010 and December 2015, with a median age of 62 (range, 31-82) years. Ninety-seven (11%) received Mel140 and 814 (89%) received Mel200. Patient and disease characteristics are summarized in Table 1. Patients in the Mel140 group had significantly higher rates of hematopoietic cell transplantation-specific comorbidity index (HCT-CI) >3 and were significantly older. Furthermore, a higher proportion of patients in the Mel140 group had Karnofsky performance status (KPS) <90, International Staging System (ISS) stages II-III, renal impairment, and less frequently had received triplet induction therapy (Table 1). In order to correct for potential bias for the impact of disease status at transplant (i.e., partial response [PR] or worse and very good partial response [VGPR] or better), we performed 1:3 (Mel140 *vs.* Mel200) propensity score matching within disease status using the variables listed in Table 2. Matching was done separately for patients with ≤PR and those with ≥VGPR at ASCT. After matching, only HCT-CI scores for patients with ≥VGPR 1st transplant remained significantly different between the two melphalan groups (Table 2). The median age of the matched patients was 69 (range, 43-81) years.

With a median follow-up of 54.6 (range, 0.3-112.2) months of all study patients, the median PFS and OS were 39.6 (95% confidence interval [CI]: 36.7-43.8) and 92.0 (95% CI: 85.0-101.1) months, respectively. At the time of transplant, 52% had ≥VGPR in the Mel140 group compared to 50% in the Mel200 group (*P*=0.75). At 3 months after transplant, the response rates were similar between the two melphalan groups (*P*=0.23). The complete response (CR)/stringent CR (sCR), VGPR, and PR rates were 26%, 49%, and 20%, respectively, in the Mel140 group, compared to 29%, 46%, and 22%,

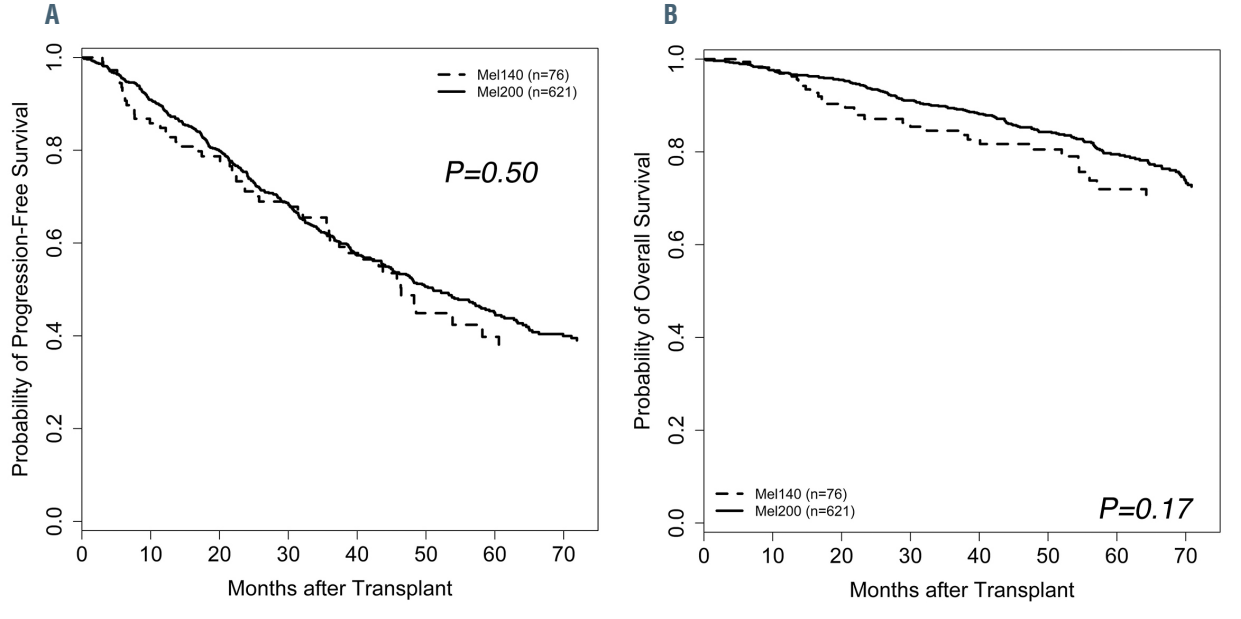

Figure 1. Kaplan-Meier survival curves of multiple myeloma patients treated with either Mel140 (dashed lines) or Mel200 (solid lines) conditioning prior to autologous stem cell transplantation. (A) Progression-free survival; (B) overall survival. Mel140: intermediate dose of melphalan 140 mg/m^2; Mel200: high dose of melphalan 200 mg/m^2.

respectively, in the Mel200 group. The median PFS and OS in the Mel140 group were 36.6 (95% CI: 26.3-43.7) and 83.0 (95% CI: 55.3-not reached) months, respectively, compared to 40.6 (95% CI: 37.0-45.1) and 92.0 (95% CI: 86.2-101.7) months, respectively, in the Mel200 group. Before adjusting for the known risk factors, Mel200 was associated with comparable PFS (hazard ratio [HR]: 0.81, 95% CI: 0.63-1.05; *P*=0.12), but improved OS (HR: 0.62, 95% CI: 0.44-0.87; *P*=0.005). After adjusting for age at ASCT, ISS, KPS, serum creatinine, disease status at ASCT, HCT-CI, and induction treatment, there were no statistically significant differences in PFS (HR 0.91, 95% CI: 0.66-1.26; *P*=0.58) or OS (HR: 0.79, 95% CI: 0.52-1.19; *P*=0.26) between the Mel140 (reference) and Mel200 groups (Figure 1).

The 1:3 matching produced a dataset of 304 patients, 76 in the Mel140 group and 228 in the Mel200 group. The response rates at 3 months after ASCT were similar to the estimates before matching (Mel140: 96%; Mel200: 96%). The CR/sCR, VGPR, and PR rates were 24%, 53%, and 20%, respectively, in the Mel140 group, compared to 30%, 49%, and 18%, respectively, in the Mel200 group. At a median follow-up of 51.8 (range: 0.3-105.1) months, the median PFS and OS for all matched patients were 38.3 (95% CI: 33.5-43.5) and 82.2 (95% CI: 73.0-97.9) months, respectively. Using fitted conditional regression models, the overall PFS (HR: 0.90, 95% CI: 0.63-1.29; *P*=0.56) and OS (HR: 0.72, 95% CI: 0.46-1.13; *P*=0.15) were not significantly different between the two melphalan groups. Likewise, there were no significant differ-

Table 1. Patient and disease characteristics by melphalan dose for all patients.

Measure, n (%)	Melphalan Dose 140 mg (N=97)	200 mg (N=814)	*P*
Age at ASCT			
< 65 years	20 (21)	562 (69)	< 0.001
≥ 65 years	77 (79)	252 (31)	
Sex			
Male	56 (58)	465 (57)	1.00
Female	41 (42)	349 (43)	
ISS stage			
I	15 (19)	299 (44)	< 0.001
II	34 (43)	197 (29)	
III	31 (39)	182 (27)	
Unknown	17	136	
Cytogenetic risk*			
Standard	67 (74)	599 (77)	0.43
High	24 (26)	176 (23)	
Unknown	6	39	
Disease status at ASCT			
PR or worse	47 (48)	411 (50)	0.75
VGPR or better	50 (52)	403 (50)	
LDH			
Normal	50 (85)	459 (88)	0.40
High	9 (15)	61 (12)	
Unknown	38	294	
Creatinine			
< 2 mg/dL	61 (68)	653 (85)	< 0.001
≥ 2 mg/dL	29 (32)	116 (15)	
Unknown	7	45	
Karnofsky performance status			
< 90	38 (40)	180 (23)	0.001
≥ 90	58 (60)	597 (77)	
Unknown	1	37	
HCT-CI			
≤ 3	53 (55)	645 (81)	< 0.001
> 3	43 (45)	156 (19)	
Unknown	1	13	
Induction treatment			
Conventional	1 (1)	19 (2)	0.012
IMiD	11 (11)	73 (9)	
PI	47 (48)	272 (33)	
IMiD + PI	38 (39)	450 (55)	
Maintenance therapy			
No	24 (25)	183 (22)	0.61
Yes	73 (75)	631 (78)	

ASCT: autologous stem cell transplantation; HCT-CI: hematopoietic cell transplantation-specific comorbidity index; IMiD: immunomodulatory imide drug; ISS: International Staging System; LDH: lactate dehydrogenase; PR: partial response; PI: proteasome inhibitor; VGPR: very good partial response. *High-risk cytogenetic category was defined as patients with any of the following genetic abnormalities at diagnosis: 17p deletion, t(4;14), t(14;16), 1q gain, and del13 (only if by cytogenetics).

ences in CIR (HR: 0.88, 95% CI: 0.65-1.20; *P*=0.43) or NRM (HR 1.39, 95% CI: 0.61-3.16; *P*=0.43) between the two groups.

In the matched cohort with ≤PR at ASCT (n=140), there was a trend for improved OS (HR: 0.53, 95% CI: 0.28-1.02; *P*=0.06) for the Mel200 group, but not in PFS (HR: 1.01, 95% CI: 0.60-1.71; *P*=0.97), CIR (HR: 0.97, 95% CI: 0.63-1.49; *P*=0.90), or NRM (HR: 0.84, 95% CI: 0.30-2.37; *P*=0.74). In patients with ≥VGPR at ASCT (n=164), there were no statistical differences between the two melphalan groups in OS (HR: 0.93, 95% CI: 0.49-1.75; *P*=0.82), PFS (HR: 0.82, 95% CI: 0.49-1.36; *P*=0.43), CIR (HR: 0.81, 95% CI: 0.52-1.27; *P*=0.36), or NRM (HR: 2.41, 95% CI: 0.60-9.64; *P*=0.21).

Hematological toxicities were universal as expected and there were no significant differences in either neutrophil or platelet engraftments between the two groups. Gastrointestinal toxicity of any grade was the most commonly reported side effect, observed in 91% and 96% of Mel140 and Mel200 patients, respectively (*P*=0.13). Mucositis rates were significantly higher with Mel200 (49%) compared to Mel140 (29%; *P*=0.002). The majority were grades 1-2, 26% in the Mel140 group and 48% in the Mel200 group. A higher percentage of patients in the Mel200 group had febrile neutropenia (34% *vs.* 25%; *P*=0.20), but the documented infection rates were comparable (25% in the Mel200 group *vs.* 26% in the Mel140 group; *P*=0.88). Renal toxicity was observed more frequently in the Mel140 group (5% *vs.* 2%; *P*=0.11); this was expected because even after matching, higher proportion of patients in this group had renal impairment.

Other non-hematological toxicities were less frequent. Higher rate of cardiac toxicity in the Mel140 group (8% in the Mel140 group *vs.* 3% in the Mel200 group; *P*=0.10). The rates of grades 3-4 non-hematological toxicities for the 304 matched patients were 33% for Mel140 and 22% for Mel200 (*P*=0.09). During the study period, 33 of the 76 patients in the Mel140 group and 89 of the 228 patients in the Mel200 group died. The most common cause of death was relapse/recurrent disease (81% for both Mel140 and Mel200; *P*=1.00). The 1-year NRM was 1% in the Mel140 group, compared to 3% in the Mel200 group (*P*=0.64).

In this study, we found that a reduced dose of Mel140 is feasible for use in older MM patients and those considered ineligible for Mel200. In patients with VGPR or better at transplant, use of Mel140 had comparable response rates, PFS, and OS to Mel200. In patients with ≤PR at ASCT, there was a trend towards improved OS with Mel200.

Table 2. Patient and disease characteristics by melphalan dose for matched patients.

	PR or worse			VGPR or better		
Measure, n (%)	Mel140 (N=35)	Mel200 (N=105)	*P*	Mel140 (N=41)	Mel200 (N=123)	*P*
Age at ASCT						
< 65 years	5 (14)	20 (19)	0.62	7 (17)	26 (21)	0.66
≥ 65 years	30 (86)	85 (81)		34 (83)	97 (79)	
Sex						
Male	22 (63)	69 (66)	0.84	25 (61)	71 (58)	0.85
Female	13 (37)	36 (34)		16 (39)	52 (42)	
ISS stage						
I	6 (17)	35 (33)	0.16	8 (20)	33 (27)	0.45
II	12 (34)	33 (31)		19 (46)	44 (36)	
III	17 (49)	37 (35)		14 (34)	46 (37)	
Cytogenetic risk						
Standard	23 (70)	77 (75)	0.50	26 (67)	81 (71)	0.69
High	10 (30)	25 (25)		13 (33)	33 (29)	
LDH						
Normal	20 (87)	68 (92)	0.44	27 (87)	80 (89)	0.75
High	3 (13)	6 (8)		4 (13)	10 (11)	
Creatinine						
< 2 mg/dL	22 (63)	80 (76)	0.13	29 (71)	93 (76)	0.54
≥ 2 mg/dL	13 (37)	25 (24)		12 (29)	30 (24)	
Karnofsky performance status						
< 90	14 (40)	27 (26)	0.13	17 (41)	38 (31)	0.25
≥ 90	21 (60)	78 (74)		24 (59)	85 (69)	
HCT-CI						
≤ 3	21 (60)	71 (68)	0.42	20 (49)	87 (71)	0.014
> 3	14 (40)	34 (32)		21 (51)	36 (29)	
Induction treatment						
Conventional	1 (3)	3 (3)	0.43	0	2 (2)	0.40
IMiD	7 (20)	12 (11)		1 (2)	7 (6)	
PI	17 (49)	48 (46)		20 (49)	42 (34)	
IMiD + PI	10 (29)	42 (40)		20 (49)	72 (59)	
Maintenance therapy						
No	6 (17)	23 (22)	0.64	11 (27)	37 (30)	0.84
Yes	29 (83)	82 (78)		30 (73)	86 (70)	

ASCT: autologous stem cell transplantation; HCT-CI: hematopoietic cell transplantation-specific comorbidity index; IMiD: immunomodulatory imide drug; ISS: International Staging System; LDH: lactate dehydrogenase; Mel: melphalan; PR: partial response; PI: proteasome inhibitor; VGPR: very good partial response.

These two regimens have not been compared in randomized clinical trials, but few studies reported conflicting results.[9-12] In a small non-randomized prospective study for patients older than 65 years, there was a trend for inferior PFS and OS for patients who received Mel140.[9] In contrast, three recent studies reported comparable outcomes between the two regimens. The Mayo group reported no significant differences in survival estimates by melphalan dose intensity in older patients, despite observing improved post-transplant response rates with Mel200.[11] The study by Katragadda *et al*. showed comparable response and survival outcomes for Mel140 *versus* Mel200.[10] In a recent study by the EBMT group that provides the largest analysis of outcomes between the two melphalan doses,[12] Mel200 was found to be associated with better outcomes only in patients with <PR at the time of ASCT. In contrast, Mel140 was associated with a better OS in patients transplanted in >VGPR.

Our results from this large single center study further indicate that Mel140 has comparable efficacy to Mel200. Consistent with the EBMT results, we found that Mel140 can be particularly beneficial for patients who have achieved VGPR or better at ASCT. Of importance to note, the majority of patients in our study were (after matching) older (median age, 69 years) and/or with comorbidities. Hence, our findings might not be generalizable for younger fit patients. Furthermore, 46% of patients in the Mel140 group had an HCT-CI >3. Despite older age and medical comorbidities, the use of Mel140 was generally well-tolerated in this high-risk population. Mel140 was associated with less gastrointestinal toxicities and significantly less mucositis. Patients in the Mel140 group, despite matching, had higher rates of renal insufficiency and worse KPS, in addition to higher HCT-CI. All of these characteristics may have contributed to higher grades 3-4 non-hematological toxicities, when compared to Mel200. However, even with these adverse baseline characteristics, there was no increase in treatment-related mortality in patients who received Mel140. Besides the impact of dose intensity on the increased toxicity, the melphalan dosing in our study was fixed based on the body surface area, as opposed to pharmacokinetic-directed dosing, which could have potentially lead to inter-patient differences in their exposure to mephalan and hence a variability in the associated safety and efficacy profile.

Our study has the predictable limitations of a retrospective analysis, including patient selection and missing data, such as revised ISS (R-ISS) stage and minimal residual disease status, the use of which were limited during the study period. In order to overcome some of these limitations, we limited the study period to patients transplanted after 2010 and used a propensity matched scoring model to account for most of the known risk factors that may influence the outcomes. Furthermore, the results were reproduced by a second analytic method using multivariable regression models fit on all patients and adjusting for the same variables that were used in the matched cohort.

In conclusion, in this large, single-center matched analysis of a homogeneous patient population with MM we showed that Mel140 has comparable efficacy to Mel200, particularly in older patients and those with VGPR or better at the time of transplant.

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