Busulfan plus melphalan versus high-dose melphalan as conditioning regimens in autologous stem cell transplantation for newly diagnosed multiple myeloma

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Background
High-dose melphalan (HDMEL) represents the standard conditioning regimen before autologous stem cell transplant (ASCT) in multiple myeloma (MM), but recent updates have suggested combination of melphalan with bulsulfan (BUMEL) is also associated with favorable outcomes. We performed the current study to address the lack of comparative studies between the two conditioning regimens in Asian populations.

Methods
Using the Korean National Health Insurance and Korean Health Insurance Review and Assessment Service databases, 1,304 patients newly diagnosed with MM undergoing ASCT between January 2010 and December 2014 were identified. Patients were divided according to conditioning regimen (HDMEL vs. BUMEL), and after case matching, 428 patients undergoing HDMEL conditioning were compared to 107 patients undergoing BUMEL conditioning with respect to clinical course and treatment outcomes.

Results
The 3-year progression-free survival (PFS) was 52.5% for the HDMEL conditioning group versus 70.3% for the BUMEL conditioning group (P=0.043). The 3-year overall survival (OS) was 82.0% versus 83.5% (P=0.525), respectively. Although not statistically significant, BUMEL conditioning was associated with more platelet transfusion, while HDMEL was associated with more granulocyte colony stimulating factor support. In multivariate analysis, BUMEL conditioning was not inferior to HDMEL conditioning in regard to both PFS and OS.

Conclusion
Our study confirmed that BUMEL is an effective and well-tolerated alternative to HDMEL conditioning, with better PFS.

Key Words   Multiple myeloma, Conditioning regimen, Autologous stem cell transplantation, Busulfan, Melphalan

INTRODUCTION

The advent of various novel agents, including the new generation of proteasome inhibitors and immunomodulatory drugs, has significantly improved the median survival of patients with multiple myeloma (MM) [1]. Nevertheless, upfront autologous stem cell transplantation (ASCT) remains an integral part of MM treatment, especially for patients younger than 65 years old [2, 3]. Several strategies focusing on different aspects of the ASCT process have been proposed to achieve better overall outcomes. The most extensively developed approach is intensification of the induction regimen administered before ASCT by means of incorporating and combining newer agents [4]. Unfortunately, the median duration of response remains shorter than 4 years even with novel agent induction, and most patients inevitably experience progression [5, 6]. The administration of maintenance therapy following ASCT has also received a great deal of attention in recent years [7-13]. Thalidomide [11] and lenali-

domide maintenance [12, 13] have consistently shown improved survival [11]. In the real world, however, the use of these agents is somewhat limited in light of their toxicity, as well as financial concerns.

The final strategy, an approach not as extensively explored, is to enhance the immediate pre-transplantation conditioning regimen by either increasing the dose of melphalan or adding another agent. Either melphalan 200 mg/m^2 or high-dose melphalan (HDMEL) is the current standard conditioning regimen [14]. Only a handful of alternatives have been studied, and while most failed to show convincing superiority over HDMEL, combined busulfan and melphalan (BUMEL) has shown encouraging results [15-19]. We designed the present study to investigate the efficacy and clinical outcomes of BUMEL conditioning in Korean patients with MM undergoing upfront ASCT.

MATERIALS AND METHODS

Medical insurance is provided in a universal form in Korea. The National Health Insurance (NHI) program, operated by the Korean Ministry for Health and Welfare, is the sole and mandatory insurance system, covering approximately 98% of the overall Korean population [20]. Meanwhile, the Korean Health Insurance Review and Assessment Service (HIRA) is a government-affiliated organization responsible for insurance claims review and quality control of the NHI. Since the Korean population itself is fairly ethnically homogeneous, both the NHI and HIRA databases can be readily used for nationwide analyses. For the present study, we utilized information from the HIRA and NHI databases to identify adult patients with MM undergoing upfront ASCT between January 2010 and December 2014. Adult patients were defined as those ≥18 years old. We extracted data including patient demographics, time from MM diagnosis to ASCT, bortezomib exposure prior to ASCT, parameters related to ASCT including conditioning regimen and year of ASCT, and survival. Because drugs used as a part of clinical trials are not covered by the NHI, we assumed that patients receiving any treatment within 3 months of MM diagnosis were likely to have participated in clinical trials, and these patients were thus excluded from the study. Patients undergoing tandem transplantation were also excluded. Initially, 1,197 patients undergoing HDMEL conditioning and 107 patients undergoing BUMEL (intravenous busulfan) conditioning were identified. After case matching according to age, gender, year of ASCT, and bortezomib exposure prior to ASCT, 428 patients undergoing HDMEL conditioning and 107 patients undergoing BUMEL conditioning were enrolled for final analyses.

Overall survival (OS) and progression-free survival (PFS) curves were estimated using the Kaplan-Meier method. OS was defined as the time from the date of ASCT to death from any cause. PFS was derived from the date of ASCT to that of progression/relapse, or death from any cause. Transplantation-related mortality (TRM) was defined, tentatively, as death occurring within 100 days of ASCT. Univariate and multivariate proportional hazards regression models were used to identify independent risk factors for survival by means of Cox proportional hazards models. Factors associated with ASCT prognosis were included in multivariate analysis. Differences between groups were assessed using Student's t-test or one-way analysis of variance for continuous variables, and Pearson's chi-square test for categorical variables, as indicated. All analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA). P-values of <0.05 were considered statistically significant. This study was conducted according to the ethical standards of the Declaration of Helsinki and was approved by the institutional review board of Seoul National University Hospital. All authors had access to the study data and reviewed and approved this study.

Table 1. Clinical characteristics.

	Total (N, %)	HDMEL (N, %)	BUMEL (N, %)	P [b]
N	535	428	107	
Age (yr)[a]	55.8 (6.5)	55.9 (6.4)	55.3 (6.9)	0.366
Gender (male)	314 (58.7)	248 (57.9)	66 (61.7)	0.482
Year of ASCT				
2010	10 (1.9)	8 (1.9)	2 (1.9)	0.983
2011	25 (4.7)	19 (4.4)	6 (5.61)	
2012	98 (18.3)	79 (18.5)	19 (17.8)	
2013	164 (36.3)	154 (36.0)	40 (37.4)	
2014	208 (38.9)	168 (39.3)	40 (37.4)	
Bortezomib exposure prior to ASCT	169 (31.6)	132 (30.8)	37 (34.6)	0.832
MM diagnosis to ASCT (days)[a]	277.6 (398.5)	275.3 (355.7)	286.9 (538.8)	0.452
FU duration (days)[a]	449.8 (332.9)	449.4 (337.6)	451.2 (315.1)	0.960

[a]Data presented as mean (±standard deviation). [b]P-values were calculated for HDMEL versus BUMEL.
Abbreviations: ASCT, autologous stem cell transplantation; BUMEL, busulfan plus melphalan; FU, follow-up; HDMEL, high-dose melphalan; MM, multiple myeloma.

RESULTS

Clinical characteristics

The baseline characteristics of the enrolled patients are shown in Table 1. The mean age for the total cohort was 55.8 years, and the mean time from MM diagnosis to ASCT was 277.6 days (approximately 9.3 mo). About one-third of the patients were exposed to bortezomib prior to ASCT.

Outcomes and toxicity

The outcomes of ASCT are shown in Table 2. Patients undergoing BUMEL conditioning consistently showed better PFS than those undergoing HDMEL conditioning. The 3-year

PFS for BUMEL group was 70.3% compared to 52.5% for the HDMEL group (P=0.043). This result translated into better PFS overall, as seen in Fig. 1B, and the median PFS for BUMEL was not reached while the median PFS for HDMEL was 1,000 days (P=0.0351). On the other hand, the OS did not differ between the 2 groups. The 3-year OS for BUMEL was 83.5%, while it was 82.0% for HDMEL 82.0% (P=0.525), and no differences were observed between the survival curves, as shown in Fig. 1A.

There were 3 cases of TRM in HDMEL group. Patients in HDMEL group also required more granulocyte colony stimulating factor (G-CSF) support. Meanwhile, patients in BUMEL group were associated with longer hospitalization duration compared to those in HDMEL group (28.5 days vs. 25.3 days, respectively, P=0.002), and more platelet transfusion.

On multivariate analyses (Table 3), only the history of bortezomib exposure was recognized as an independent prognostic factor of OS. Conditioning regimen was not associated with survival differences, indicating BUMEL was not inferior to HDMEL with regards to both PFS and OS.

Table 2. Outcomes of autologous stem cell transplantation.

	HDMEL (N, %)	BUMEL (N, %)	P
Hospitalization duration (days)[a]	25.3 (8.7)	28.5 (8.2)	0.002
TRM	3 (0.7)	0	1.000
Toxicity			
Thrombocytopenia requiring tf[b]	19 (4.4)	9 (8.4)	0.099
Neutropenia requiring G-CSF[b]	49 (11.5)	6 (5.6)	0.075
Survival			
3-year OS	82.0	83.5	0.525
3-year PFS	52.5	70.3	0.043

[a]Data presented as mean (±standard deviation). [b]The number represents the number of patients requiring platelet transfusion or G-CSF support, respectively.
Abbreviations: BUMEL, busulfan plus melphalan; G-CSF, granulocyte colony stimulating factor; HDMEL, high-dose melphalan; OS, overall survival; PFS, progression-free survival; tf, transfusion; TRM, transplantation-related mortality.

DISCUSSION

Despite recent advances in MM treatment, upfront ASCT in fit patients is a prerequisite for long-term disease control. Opportunities to optimize the outcomes of ASCT exist at all stages throughout the process, including induction, conditioning, and maintenance. Several improvements in the induction and maintenance regimens have been established, but few studies have focused on improving conditioning regimens. These previous studies have proposed BUMEL as an attractive alternative to HDMEL to achieve maximum anti-myeloma capacity [16-19]. In the present study, we sought to explore the role of the addition of busulfan in an often under-represented Asian population, as a significant
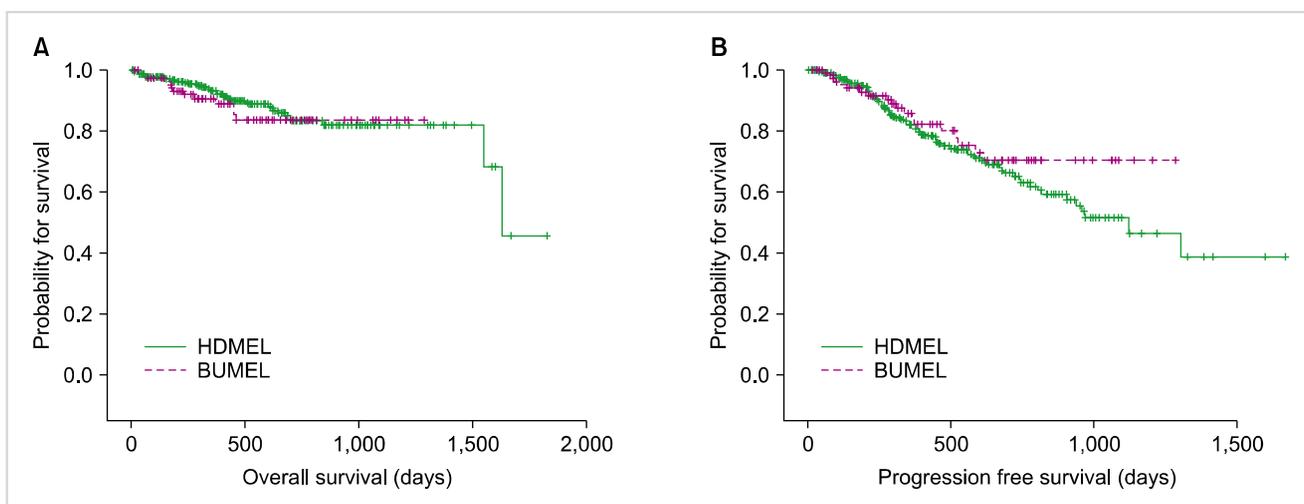

Fig. 1. (A) Overall survival compared between patients receiving high-dose melphalan conditioning regimen and patients receiving melphalan plus busulfan regimen (P=0.506). (B) Progression-free survival compared between the 2 groups (P=0.0351). MEL, HDMEL; Others, BUMEL.

Table 3. Multivariate analysis for progression-free survival and overall survival.

	OS		PFS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥60 vs. <60)	1.006 (0.965–1.048)	0.789	1.007 (0.979–1.036)	0.608
MM diagnosis to ASCT (days)	1.000 (0.999–1.000)	0.469	1.000 (0.999–1.000)	0.312
Conditioning regimen (BUMEL vs. HDMEL)	1.178 (0.630–2.202)	0.608	0.740 (0.452–1.212)	0.232
Bortezomib exposure prior to ASCT (yes vs. no)	2.733 (1.490–5.013)	0.001	0.978 (0.617–1.550)	0.924

Abbreviations: ASCT, autologous stem cell transplantation; BUMEL, busulfan plus melphalan; CI, confidence interval; HDMEL, high-dose melphalan; HR, hazard ratio; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival.

Table 4. Efficacy of busulfan-based conditioning regimen for autologous stem cell transplantation in multiple myeloma patients.

Ref	Ethnicity	HDMEL				BUMEL			
		Sample size (N)	CR (%)	Median OS (mo)	Median PFS (mo)	Sample size (N)	CR (%)	Median OS (mo)	Median PFS (mo)
Lahuerta *et al*. [16]	Spanish	472	45	46	22	186	51	57	30
Blanes *et al*. [17]	Spanish	102	49	63	24	51	61	66	33
Lahuerta *et al*. [18]	Spanish	542	53	71	31	225	51	79	41
Ria *et al*. [19]	Italian	16	38	108	97	14	79	126	121
Present	Korean	428	NA	53	33	107	NA	NR	NR

Abbreviations: BUMEL, busulfan plus melphalan; CR, complete remission; HDMEL, high-dose melphalan; NA, not available; NR, not reached; OS, overall survival; PFS, progression-free survival.

correlation between glutathione S-transferase (GST) genotype and busulfan clearance exists [21], and the frequency of GST polymorphisms is higher in Asians [22, 23]. Our findings, similar to the results of previous studies (Table 4), showed that BUMEL conditioning was associated with longer PFS compared to HDMEL conditioning. The advantage of BUMEL in extending PFS did not translate into OS improvement, probably because as MM is a longstanding disease, OS is dependent on the effects of subsequent lines of salvage treatment. Patterns of hematopoietic recovery varied between the 2 groups, with patients in the HDMEL group requiring more G–CSF support and those in the BUMEL group requiring more platelet transfusion, but the differences did not reach statistical significance.

One major pitfall of our study is the lack of details regarding patient characteristics and treatment courses. Our analyses were restricted to the limited range of information available from the national databases. Consequently, responses to ASCT and the role of maintenance treatment could not be estimated. However, some of the missing parameters can be estimated. For example, although information regarding disease control status prior to ASCT is unknown, it is safe to assume that all patients showed partial or better response to induction treatment following the strict reimbursement regulations. Also, owing to the almost uniform insurance coverage of therapeutic agents used for MM treatment, it is likely that most patients received somewhat stereotyped treatment. Thus, we would like to point out that despite its retrospective nature, our study was conducted in a some-

what homogeneous setting. Furthermore, considering the scarcity of data from Asian populations, the importance of our findings is not diminished.

In conclusion, our study suggest BUMEL conditioning regimen for newly diagnosed MM patient undergoing upfront ASCT is an attractive alternative to HDMEL conditioning regimen in Korean population.

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Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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