Busulfan plus melphalan *versus* melphalan alone conditioning regimen after bortezomib based triplet induction chemotherapy for patients with newly diagnosed multiple myeloma

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Abstract

Background: High dose melphalan (HDMEL) is considered the standard conditioning regimen for autologous stem cell transplantation (ASCT) in multiple myeloma (MM) patients. Recent studies showed superiority of busulfan plus melphalan (BUMEL) compared to HDMEL as a conditioning regimen. We compared the efficacy of HDMEL and BUMEL in newly diagnosed Asian MM patients, who are often underrepresented.

Methods: This is a single-center, retrospective study including MM patients who underwent ASCT after bortezomib-thalidomide-dexamethasone (VTD) triplet induction chemotherapy between January 2015 and August 2019.

Result: In the end, 79 patients in the HDMEL group were compared to 31 patients in the BUMEL group. There were no differences between the two groups with regards to sex, age at ASCT, risk group, and stage. The HDMEL group showed better response to pre-transplant VTD compared to BUMEL, but after ASCT the BUMEL group showed better overall response. In terms of progression-free survival (PFS), although BUMEL showed trends towards better PFS regardless of pre-transplant status and age, the difference did not reach statistical significance. The BUMEL group more often experienced mucositis related to chemotherapy, but there was no difference between the two groups with regards to hospitalization days, cell engraftment, and infection rates.

Conclusion: BUMEL conditioning deserves attention as the alternative option to HDMEL for newly diagnosed MM patients, even in the era of triplet induction chemotherapy. Specifically, patients achieving very good partial response (VGPR) or better response with triplet induction chemotherapy might benefit the most from BUMEL conditioning. Tailored conditioning regimen, based on patient's response to induction chemotherapy and co-morbidities, can lead to better treatment outcomes.

Keywords: autologous stem cell transplantation, busulfan, conditioning regimen, melphalan, multiple myeloma

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Introduction

With the advent of various novel agents, including a new generation of proteasome inhibitors and immunomodulatory drugs (IMiD), multiple myeloma (MM) outcomes have consistently improved over the years.[1,2] Even so, autologous stem cell transplantation (ASCT) remains an integral part of MM treatment, especially for

newly diagnosed patients.[3,4] Several strategies regarding different steps of the ASCT process have been proposed for better overall outcomes. The most extensively studied approach involves intensifying the induction of chemotherapy before ASCT by incorporating and combining newer agents.[3] Maintenance therapy following ASCT with lenalidomide has received an equal amount of attention in recent years and has successfully prolonged progression-free survival (PFS) and overall survival (OS).[5] The final strategy is to enhance the pre-transplantation conditioning regimens. Melphalan $200\,mg/m^2$ or high dose melphalan (HDMEL) is the current standard conditioning regimen.[6] However, there has been continuous efforts to improve the efficacy of conditioning regimen. While most approaches have failed to show convincing superiority over HDMEL, bulsulfan combined with melphalan (BUMEL) has demonstrated encouraging results.[7,8] Specifically, a prospective randomized trial curated at MD Anderson has shown significant PFS gain with BUMEL (64.7 months) compared to HDMEL (43.5 months, $p = 0.022$). However, this was at the cost of significantly increased toxicities; namely, mucositis, diarrhea, and neutropenic fever.[8] Also, for this study heterogeneous induction regimens were used.

Asian patients tend to show a higher incidence of hematological and non-hematological adverse events (AEs) following chemotherapy.[9] It is, therefore, hard to predict the impact of adding busulfan, a drug already known for variable metabolism depending on ethnicities,[10,11] in Asian populations based on the aforementioned studies. Recognizing the paucity of data comparing HDMEL and BUMEL in Asian patients in terms of efficacy and safety, we conducted this study. Homogeneously Korean patients undergoing same triplet induction regimen (VTD, bortezomib-thalidomide-dexamethasone) were included to concentrate on the role of conditioning regimen on ASCT outcomes.

Patients and methods

Study design and subjects
This was a single-center, retrospective, longitudinal cohort study of newly diagnosed active MM patients over 18 years old. The study period was set between January 2016 and August 2019.

ASCT eligible patients, defined as those under the age of 65 years according to the national insurance coverage restrictions and who received VTD as first-line treatment were enrolled. Initially, 173 patients were screened; 36 patients were excluded for undergoing induction other than VTD, 15 patients for conditioning with thiotepa based regimen, and 21 patients for receiving the second ASCT. Finally, a total of 110 patients (79 HDMEL *versus* 31 BUMEL) were identified. Their medical records were reviewed for demographics, disease characteristics, response to treatment, factors related to ASCT, AEs, and survival outcomes.

This study was conducted according to the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-1906-001-103). Informed consent was waived in light of the retrospective nature of the study and the anonymity of the subjects.

Details of VTD chemotherapy and ASCT
Patients were treated with 28-day cycles of VTD: bortezomib $1.3\,mg/m^2$ (days 1, 4, 8, 11), thalidomide 100 mg/day (days 1–28), and dexamethasone 40 mg (days 1–4, days 9–12). Depending on tolerability, 4–6 cycles of VTD were delivered prior to ASCT. Upon achieving PR or better response, stem cell mobilization was carried out using granulocyte colony-stimulating factor (G-CSF) ± plerixafor. Chemo-mobilization using cyclophosphamide $3\,g/m^2$ was used in selected patients per attending physician's choice. When white blood cell count reached $\geqslant 10/\mu l$, apheresis was begun with the goal of collecting at least 2×10^6 CD34+ cells/kg peripheral blood stem cells for a single ASCT.

The patients undergoing BUMEL conditioning received busulfan 3.2 mg/kg on days -6 through -4, followed by melphalan $70\,mg/m^2$/day on days -3 and -2.[12] The patients undergoing HDMEL conditioning received melphalan $100\,mg/m^2$/day on days -3 and -2.[6] Busulfan was infused with seizure prophylaxis using levetiracetam.

Both groups received the same supportive care in terms of prophylactic antifungals, prophylactic antibiotics, cell growth factors and cytomegalovirus (CMV) infection prophylaxis. Micafungin

was used as an prophylactic antifungal and ciprofloxacin as an prophylactic antibiotic, and these were administered from the day of the chemotherapy initiation to absolute neutrophil count (ANC) recovery. Intravenous immunoglobulin was administered as CMV prophylaxis.

Definitions

The response to therapy and disease status were defined according to the International Myeloma Working Group response criteria.[13] The overall response rate (ORR) was defined as the proportion of patients achieving at least partial response (PR). AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Transplant related morality (TRM) was defined as during the transplant procedure or the first 100 days after ASCT.

PFS was defined as the time from stem cell infusion to relapse or death from any cause. OS was defined as the time from stem cell infusion to death of any cause. Neutrophil engraftment was defined as an $ANC > 0.5 \times 10^9/L$ on three consecutive measurements. Platelet recovery was defined as seven consecutive measurements of $20.0 \times 10^9/L$ without transfusion. Responses to ASCT was checked upon engraftment. The Median time to response check was 16 days (range 10–31) from the cell infusion date.

Statistical analysis

Differences between groups were assessed using a Student's *t*-test or one-way analysis of variance for continuous variables, and Pearson chi-square test for categorical variables, as indicated. The PFS and OS curves were estimated using the Kaplan–Meier method. If patients survived without death or progression, the survival was censored at the latest date of follow-up, when no death or progression was confirmed. Associations between potential prognostic factors and survival outcomes were evaluated using the Cox's proportional hazard regression models. A stepwise backward procedure was used, and predictors achieving a *p*-value below 0.05 were considered then sequentially removed if the *p*-value in the multiple model was above 0.05. All data were analyzed using the Statistical Package for the Social Sciences software (IBM® SPSS®Statistics, version 25.0). *p-values* of <0.05 were considered statistically significant.

Results

Patient characteristics and ASCT details

The baseline characteristics of all patients are summarized in Table 1. Overall, there were no differences between the two groups regarding age at diagnosis, international staging system (ISS) and revised-international staging system (R-ISS), age at ASCT, and risk group. There were more patients achieving complete response (CR) with VTD in the HDMEL group compared to the BUMEL group (31.6 *versus* 9.7%, *p* = 0.047). Patients in the HDMEL group received more CD34 than those in the HDMEL group (4.535 *versus* $2.875 \times 10^6/kg$, *p* = 0.012). In the HDMEL group, maintenance therapy was given to two patients (2.6%), whereas in the BUMEL group 13 patients (41.9%) received maintenance therapy (*p* < 0.001).

ASCT outcomes

The outcomes of ASCT are shown in Table 2. The ORR after ASCT were similar between the HDMEL group *versus* the BUMEL group (96.2% *versus* 96.8%, respectively, *p* = 0.885). Stringent complete response (sCR) and CR after ASCT was lower in the HDMEL group compared to BUMEL group (49.4% *versus* 71.0%, respectively, *p* = 0.040). The median time to neutrophil engraftment (HDMEL 10 days *versus* BUMEL 10 days, *p* = 0.400) and platelet engraftment (HDMEL 12 *versus* BUMEL 13 days, *p* = 0.929) were similar between the two groups.

The median PFS was 29.3 months for the HDMEL group *versus* not reached for BUMEL group (*p* = 0.273, Figure 1a). The median OS was not reached in either group (*p* = 0.424, Figure 1b). Since HDMEL patients were associated with better response to induction, we further compared survival outcomes based on pre-transplant status (Figure 2). In patients initially achieving very good partial response (VGPR) or better response with induction, although the BUMEL group (not reached) showed better PFS compared to the HDMEL group (36.8 months), the difference did not reach statistical significance (*p* = 0.422). In patients who showed PR or less response to

Table 1. Baseline characteristics.

Characteristics		HDMEL (*n* = 79)	BUMEL (*n* = 31)	*p*
Age at diagnosis	Median (years, range)	56.5 (33.2–64.55)	57.0 (33.6–66.6)	0.605
Age at ASCT	Median (years, range)	56.8 (33.5–65.0)	57.6 (34.1–67.3)	0.746
Sex (%)	Male	50 (63.3)	20 (64.5)	0.904
Performance status (%)	ECOG ⩾2	15 (19.0)	0 (0.0)	0.027
ISS (%)	I	22 (27.8)	12 (38.7)	0.455
	II	28 (35.4)	8 (25.8)	
	III	23 (29.1)	8 (25.8)	
	Missing	6 (7.6)	3 (9.7)	
R-ISS (%)	I	6 (7.6)	3 (9.7)	0.669
	II	31 (39.2)	7 (22.6)	
	III	9 (11.4)	4 (12.9)	
	Missing	27 (34.2)	17 (54.8)	
Risk group (%)	High risk*	11/58 (19.0)	3/27 (11.1)	0.196
	Missing	21 (26.6)	4 (12.9)	
Response to induction (%)	sCR and CR	25 (31.6)	3 (9.7)	0.047
	VGPR	28 (35.4)	13 (41.9)	
	PR	26 (32.9)	14 (45.2)	
	SD	0 (0.0)	1 (3.2)	
Infused CD34, ×10⁶/kg		4.535 (2.090–11.830)	2.875 (2.070–7.610)	0.012
Maintenance (%)	Thalidomide	1 (1.3)	0 (0.0)	0.000
	Lenalidomide	1 (1.3)	13 (41.9)	
	None	73 (92.4)	18 (58.1)	

*High risk multiple myeloma: presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16).
ASCT, autologous stem cell transplantation; CR, complete remission; ECOG, Eastern Cooperative Oncology Group; ISS, international staging system; PR, partial response; R-ISS, revised international staging system; sCR, stringent complete remission; SD, stable disease; VGPR, very good partial response.

induction, there was no significant difference between the two groups. We also tested the effects of age (Figure 3) on survival outcomes. There was no significant difference between the two conditioning groups according to age.

On multivariate analyses, ISS and response to induction were recognized as prognostic factors for PFS (Table 3).

Toxicities
Fortunately, there were no cases of TRM in either group (Table 2). The median hospitalization days for the HDMEL group was 20 days (range 15–37 days) and for the BUMEL group 24 days (range 22–78 day; *p* = 0.178). Patients undergoing BUMEL were associated with higher incidence of any infections, especially of bacterial origin. Gastrointestinal toxicities including diarrhea and

Table 2. Outcomes of autologous stem cell transplantation.

Outcomes	HDMEL (*n* = 79)	BUMEL (*n* = 31)	*p*
Post-ASCT response			0.317
sCR and CR (%)	39 (49.4)	22 (71.0)	
VGPR (%)	26 (32.9)	5 (16.1)	
PR (%)	11 (13.9)	3 (9.7)	
SD (%)	1 (1.3)	1 (3.2)	
PD (%)	2 (2.5)	0 (0.0)	
ORR (≥PR) (%)	76 (96.2)	30 (96.8)	0.885
Time to neutrophil engraftment, days*	10 (8–52)	10 (9–13)	0.400
Time to platelet recovery, days*	12 (7–57)	13 (7–21)	0.929
Hospitalization duration, days*	20 (15–37)	24 (22–78)	0.178
Transplant related mortality	0	0	NA
Clinically documented infection (%)	5 (6.3)	4 (12.9)	0.134
Bacterial (%)	3 (3.8)	4 (12.9)	
Fungal (%)	0 (0.0)	0 (0.0)	
Viral (%)	2 (2.5)	0 (0.0)	
Gastrointestinal			0.607
Any (%)	76 (96.2)	30 (96.7)	
≥Grade 3 (%)	46 (58.2)	15 (48.4)	
Mucositis			0.002
Any (%)	36 (45.6)	26 (83.9)	
≥Grade 3 (%)	12 (15.2)	10 (32.3)	
Hepatic			0.067
Any (%)	34 (43.0)	16 (51.6)	
≥Grade 3 (%)	0 (0.0)	2 (1.8)	

*Presented as median (range).
ASCT, autologous stem cell transplantation; CR, complete remission; NA, not applicable; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete remission; SD, stable disease; VGPR, very good partial response.

nausea were the most common AEs documented in both groups. Mucositis occurred more often and more severely in the BUMEL group (any mucositis, *p* = 0.002; grade 3 or worse mucositis, *p* = 0.002). Patients in the BUMEL group also manifested more hepatic toxicities compared to those in the HDMEL group (51.6 *versus* 43.0%, *p* = 0.067).

Discussion

The purpose of this study was to evaluate efficacy and safety of BUMEL conditioning after triplet induction therapy in the East Asian population. The exact mechanism of synergism between busulfan and melphalan is not completely understood, but the difference in chemical structures of
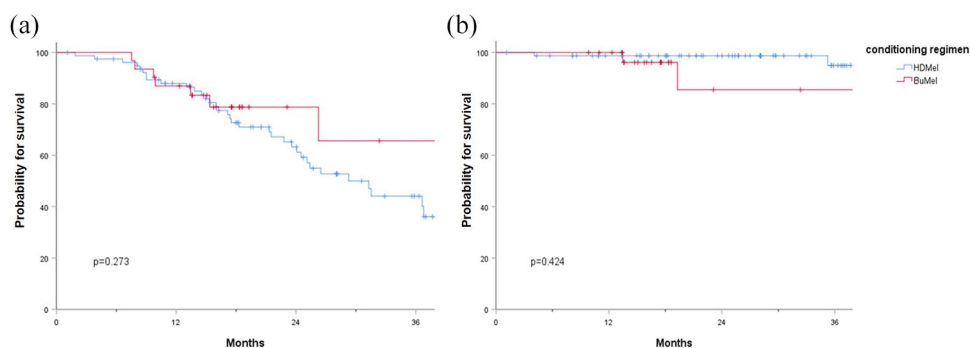
Figure 1. (a) Progression-free survival according to conditioning regimen. (b) Overall survival according to conditioning regimen.
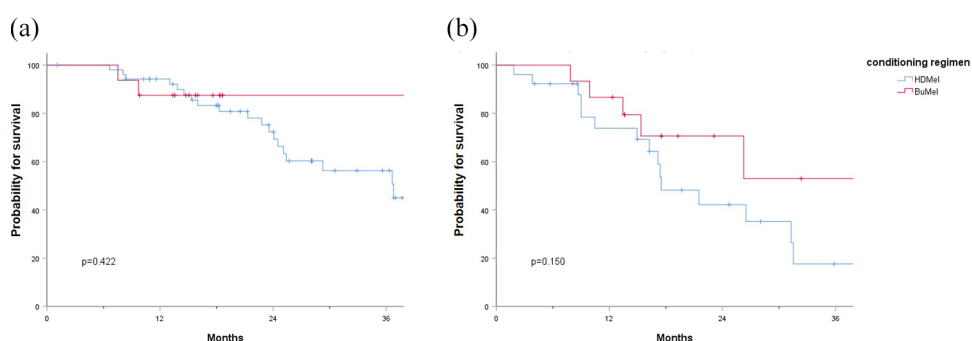

Figure 2. (a) Progression-free survival according to conditioning regimen in patients who achieved very good partial response or better response pre-transplant. (b) Progression-free survival according to conditioning regimen in patients who showed partial response or worse response pre-transplant.
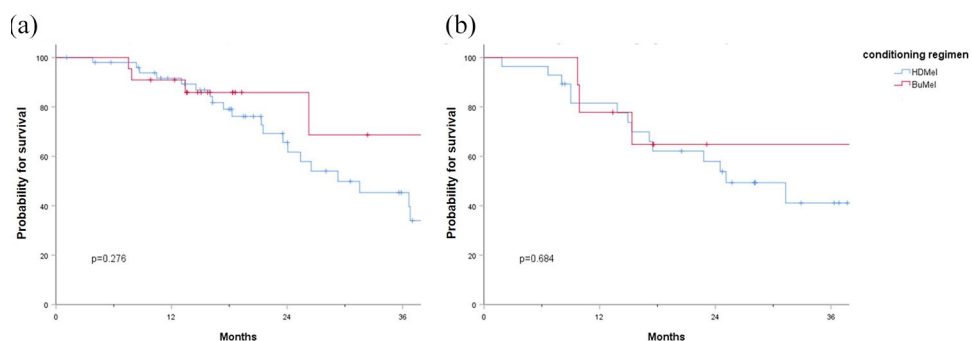

Figure 3. (a) Progression-free survival according to conditioning regimen in patients <60 years old. (b) Progression-free survival according to conditioning regimen in patients ≥60 years old.

these two alkylators suggests inherent variations in the type of DNA damage induced. These complex genomic lesions are more difficult to repair compared to the type of DNA adducts elicited by each drug alone, leading to synergistic cytotoxicity.[8] Our study, as in previous studies (Table 4), showed that BUMEL conditioning is associated with trends towards better survival regardless of pre-transplant status and age. More importantly, BUMEL seems to overcome the impediments of induction chemotherapy, as evident by higher rates of ORR post-transplant in the BUMEL

Table 3. Prognostic factors for progression-free survival (PFS).

Variables		Univariate		Multivariate	
		HR (95% CI)	p	HR (95% CI)	p
Age	<60 years	0.770 (0.413–1.436)	0.411		
Performance status	ECOG < 2	0.537 (0.222–1.300)	0.168		
ISS	I	1			
	II	2.142 (0.795–5.773)	0.132	2.708 (0.972–7.543)	0.057
	III	4.313 (1.829–10.168)	0.001	4.202 (1.740–10.150)	0.001
Risk group	High risk*	1.295 (0.535–3.132)	0.566		
Response to induction	VGPR or better	1			
	PR or worse	2.066 (1.117–3.820)	0.021	2.547 (1.273–5.095)	0.008
Maintenance	No	1			
	Yes	0.636 (0.192–2.103)	0.458		
Conditioning regimen	HDMEL	1			
	BUMEL	0.635 (0.280–1.439)	0.277		

*High risk multiple myeloma: presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16).
ECOG, Eastern Cooperative Oncology Group; ISS, international staging system; PR, partial response; R-ISS, revised-international staging system; VGPR, very good partial response.

group compared to the HDMEL group, despite the differences in pre-transplant status. Lastly, although BUMEL caused more mucositis compared to HDMEL, this did not lead to higher rates of infection or longer hospitalization days. As evidenced by a similar time duration to platelet and neutrophil engraftment, BUMEL was fairly well-tolerated in Korean patients.

The median PFS of both the HDMEL and BUMEL groups were comparable to previous studies.[8,12,14,15] One difference between our study and previous ones is that our patients uniformly underwent VTD induction, mitigating the possible confounding effects of a more potent induction regimen. Due to the relatively short follow-up duration (34.2 months for HDMEL, 22.4 months for BUMEL) the survival difference did not reach statistical difference, but higher rates of ORR were seen in BUMEL group; thus, BUMEL conditioning is worth further investigation as a

potential alternative to HDMEL conditioning for selected groups of patients. More specifically, BUMEL seems to produce more prominent effects for those achieving VGPR or better response to induction, as the plateau graph of Figure 2a suggests. Also, younger patients seem to tolerate BUMEL better than older patients, as seen in Figure 2b.

Unfortunately, BUMEL is not without faults. Our patients showed generally higher rates of hepatic toxicity, which was more prominent in the BUMEL group. Although intravenous busulfan has more predictable pharmacokinetics compared to oral busulfan, its therapeutic range is still narrow, with variable metabolism depending on ethnicity.[16–20] A glutathione S-transferase (GST) genotype is thought to correlate with busulfan clearance and thus drug toxicity.[20] Since the frequency of GST polymorphism is higher in Asians,[10,11,18,20] Asian patients could, in fact, be

Table 4. Comparative analyses with previous studies.

Study	Group	Sample size	Survival outcomes				Response (%)		Adverse events (%)		
			Median PFS, months	*p*	Median OS, months	*p*	Induction ORR/ (sCR + CR)	ASCT ORR (sCR + CR)	GI sx All (Gr⩾3)	Mucositis All (Gr⩾3)	Hepatic All (Gr⩾3)
Bashir *et al.*[8]	HDMEL	98	43.5	0.022	NR	0.750	93.8 (28.6)	96.9 (33.7)	98.0 (2.0)	49.0 (0.0)	1.0 (0.0)
	BUMEL	104	64.7		NR		96.2 (21.2)	98.1 (26.9)	93.3 (3.8)	96.2 (14.4)	32.7 (2.9)
Lahuerta *et al.*[14]	HDMEL	529	31.0	0.009	71.0	0.040	82.3 (24.6)	92.0 (53.0)	17.0 (2.1)	43.1 (6.4)	1.9 (0.0)
	BUMEL*	208	41.0		79.0		81.5 (26.5)	91.0 (51.0)	8.2 (1.0)	54.3 (10.1)	8.2 (0.5)
Blanes *et al.*[12]	HDMEL	102	24.0	0.100	63.0	0.860	92.2 (19.6)	94.1 (49.0)	12.7 (0.0)	46.0 (0.0)	0.0 (0.0)
	BUMEL	51	33.0		65.5		92.2 (19.6)	98.0 (51.0)	15.7 (0.0)	88.0 (0.0)	13.7 (0.0)
Song *et al.*[15]	HDMEL	76	25.2	0.995	70.1	0.784	93.3 (11.8)	94.7 (50.0)	76.3 (18.4)	78.9 (6.6)	48.7 (2.6)
	BUMEL	76	32.9		NR		92.1 (22.4)	92.1 (38.2)	71.1 (14.5)	72.4 (13.2)	22.4 (7.9)
Current	HDMEL	79	29.3	0.273	NR	0.424	100 (31.6)	96.2 (49.4)	96.2 (58.2)	45.6 (15.2)	43.0 (0.0)
	BUMEL	31	NR		NR		97.8 (9.7)	96.8 (71.0)	96.7 (48.4)	83.9 (32.3)	51.6 (1.8)

*Oral busulfan.
ASCT, autologous stem cell transplantation; CR, complete remission; GI, gastrointestinal; Gr, grade; NA, not applicable; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; sCR, stringent complete remission.

more susceptible to hepatotoxicity as in our study. The administration of busulfan guided by therapeutic drug monitoring could maximize BUMEL efficacy while minimizing AEs. Even so, in Korean patients with underlying liver disease, we would recommend reconsidering the use of BUMEL. All in all, adaptively choosing an individually-tailored conditioning regimen should be considered in all cases.

Recently, it was reported that the presence of clonal hematopoiesis of indeterminate potential (CHIP) in MM patients is associated with worse PFS (hazard ratio 1.45, *p* < 0.001) and OS (hazard ratio 1.4, *p* = 0.02).[21] Also, it was suggested that IMiD maintenance should be given regardless of CHIP status to improve survival. In our cohort, CHIP data was available in 14 patients (3 in the HDMEL group and 11 in the BUMEL group). Only two patients in the BUMEL group harbored DNMT3A; thus, outcome comparisons within and between the groups could not be made. However, it is worth noting that 41.9% of the BUMEL patients received IMiD maintenance, while only 2.6% of HDMEL patients received IMiD maintenance. The differences in maintenance therapy can be attributed to national insurance clearance and possibly intolerance on the part of the patients. The correlation between CHIP presence, conditioning regimen and ASCT outcomes need to be further explored.

One of the major limitations of this study is the possibility of selection bias arising from the study's retrospective nature. Conditioning regimen were chosen per the attending physician's decision, based on the patient's age, co-morbidities, performance and prior treatment tolerability; which is to say, the choice was rather subjective. However as shown in Table 1, the baseline characteristics were similar between the two groups; thus, this concern can be mitigated. Another pitfall is the lack of in-depth analysis regarding high-risk MM. Although the proportion of high-risk MM was similar between the two groups, numerically speaking there were only three patients in the BUMEL group. As a result, comparative analyses could not be performed to determine if high-risk MM patients benefit from more intensive conditioning regimen. This issue should be addressed in future studies encompassing a larger number of patients.

Conclusions

In conclusion, BUMEL conditioning deserves further investigation as an alternative option to HDMEL for newly diagnosed MM patients, even in the era of triplet induction chemotherapy. However, for Korean patients with underlying liver conditions, the use of BUMEL should be second-guessed. Individualization of the conditioning regimen, based on response to induction, co-morbidities and age, can lead to better treatment outcomes.

Authors' note

The results of this study have been presented at the 71st Fall Conference of the Korean Association of Internal Medicine, 24–25 October 2020, Republic of Korea.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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