Annals of Hematology and Oncology Research

ISSN: 2692-7950

Research Article

Busulfan, Etoposide and Cyclophosphamide *versus* High-Dose Melphalan as a Conditioning Regimen for Autologous Hematopoietic Stem Cell Transplantation in Patients with Multiple Myeloma

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Abstract

Aim: We compared the outcomes between two conditioning regimens; a combination of busulfan, etoposide and cyclophosphamide *versus* high-dose melphalan in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation.

Methods: Between August 2015 and December 2020, 78 patients with multiple myeloma (median age=52) underwent autologous hematopoietic stem transplantation using busulfan, etoposide and cyclophosphamide (n=37) or high-dose melphalan (n=41) as the conditioning regimen. Busulfan was administered intravenously at 0.8 mg/kg/day on days -7, -6 and -5; etoposide was administered intravenously at 400 mg/m^2/day on days -5 and -4, cyclophosphamide was administered intravenously at 50 mg/m2/day on days -3 and -2, and melphalan was administered intravenously at 200 mg/m2 on days -3 and -2 followed by stem cell transplantation on day 0.

Results: Overall response rate, progression-free survival, overall survival and relapse were statistically similar between the two groups. High-dose melphalan conditioning was associated with increased incidence of pulmonary toxicities (36.6% *vs.* 5.4% for busulfan, etoposide and cyclophosphamide, P=0.002).There were two cases of transplantation-related mortality, one in each group. In multivariate analysis, busulfan, etoposide and cyclophosphamide conditioning was statistically similar to high-dose melphalan conditioning in regard to progression-free survival, overall survival and relapse. But, low-risk disease stages showed to predict progression-free survival and relapse risk, with patients in International staging system I and II significantly had longer time to progression;(ISS I: hazard ratio=0.186, P=0.006 and ISS II: hazard ratio=0.240, P=0.022) and delayed time to relapse;(ISS I: hazard ratio=0.220, P=0.013, ISS II: hazard ratio=0.262, P=0.036). Beta-2-microglobulin predicted survival, with pretreated elevated beta-2-microglobulin significantly predict poor overall survival (hazard ratio=1.356, P=0.041).

Conclusion: Busulfan, etoposide and cyclophosphamide is superior to high-dose melphalan in non-hematological toxicity profile; however confer similar response rates, survival and relapse rate as high-dose melphalan in multiple myeloma patients undergoing stem cell transplantation.

Keywords: Autologous stem cell transplantation; Conditioning regimen; Multiple myeloma; Survival; Toxicities

Introduction

High-Dose Chemotherapy (HDC) followed by Autologous Hematopoietic Stem Cell Transplantation (autoHSCT) continues to be the standard consolidation treatment after induction therapy in newly diagnosed patients with MM for over two decades [1]. The benefit of autoHSCT also extends to patients with relapsed disease who remain transplant-eligible. Despite improved response rates, prolonged Progression-Free Survival (PFS), and Overall Survival (OS) associated with HDC followed by autoHSCT, disease Progression (PD), relapse and transplant-related morbidity and mortality unfortunately remain challenging in most patients [2-5].

Several strategies focusing on achieving better outcomes in the treatment of MM have been proposed. The most extensively developed approach is intensification of the induction therapy administered before autoHSCT by means of incorporating and combining newer agents [6].With the emergence of safer and more effective novel drugs such as Immunomodulatory Drugs (IMiDs), Proteasome Inhibitors (PIs) and monoclonal antibodies the outcomes have vastly improved [7,8]. Unfortunately, even with newer induction drugs, most patients inevitably experience disease progression or relapse and die from the disease [9]. The administration of maintenance therapy following autoHSCT has received a great deal of attention in recent years [10-12], and thalidomide, lenalidomide, bortezomib and ixazomib have been shown to improve PFS and OS [13-15]. However, the long-term indefinite use of these agents is limited due to their toxicity and cost, which negatively impacts the Quality of Life (QOL) and

Citation: Kimambo EH, Li LH, Ma DD, Ling Y, Miao WJ, Li WF, et al. Busulfan, Etoposide and Cyclophosphamide *versus* High-Dose Melphalan as a Conditioning Regimen for Autologous Hematopoietic Stem Cell Transplantation in Patients with Multiple Myeloma. Ann Hematol Oncol Res. 2022; 2(1): 1012.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Mar 14th, 2022

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limits the duration of administration. A final strategy to improve outcomes after autoHSCT is based on using a safer and more effective pre-transplantation conditioning regimen. High-Dose Melphalan (HDM) at a dose of 200 mg/m^2 (MEL200), is the current international standard conditioning before autoHSCT for MM patients younger than 65 years old [16].

In an effort to improve the outcomes of autoHSCT and decrease the high incidence of regimen-related toxicity, other chemotherapy and chemo-radiotherapy conditioning regimens have been used in preparation for autoHSCT, but failed to show convincing superiority over HDM. A combination of busulfan, etoposide and cyclophosphamide (BVC) has shown encouraging results when used as a conditioning regimen followed by autoHSCT in patients with malignant lymphoma [17] and MM [18-21]. We designed the present retrospective study from three institutions to investigate and compare the efficacy, outcomes and survival of the patients from using either BVC or HDM as a conditioning regimen in newly diagnosed and relapsed patients with MM undergoing autoHSCT.

Patients and Methods

Patient selection

Between August 2015 and December 2020, 78 patients aged 29-65 (median age=52) years with MM who received HDC followed by autoHSCT from three institutions were retrospectively reviewed. Inclusion criteria included adults (aged 18-65 years) with MM who had serum creatinine level of <2.0 mg/dL, without active infections or severe obstructive and/or restrictive pulmonary disease determined by pulmonary function testing (ie, diffusing capacity of the lung for carbon monoxide (DLCO) <50% and/or Forced Expiratory Volume (FEV) <50% and/or Forced Vital Capacity (FVC) <50%), cardiac Ejection Fraction (EF) >40% and Karnofsky Performance Status (KPS) ≥ 70. Thirty seven patients underwent autoHSCT following conditioning with BVC, whereas 41 patients underwent autoHSCT following conditioning with HDM.

The diagnosis of MM was made using the updated 2014 International Myeloma Working Group (IMWG) criteria [22] and staging of International Staging System (ISS) [23]. Evaluation of disease responses was performed 1-3 months after transplantation, according to Autologous Bone Marrow Transplantation Registry response criteria [24]. OS was defined as time from the date of autoHSCT to death from any cause.PFS was defined as time from the date of autoHSCT to that of disease progression or death. Transplantation-Related Mortality (TRM) was defined as death due to complication (other than relapse) occurring within 100 days of autoHSCT. Neutrophil and platelet engraftment were defined as the first of 3 days with an Absolute Neutrophil Count (ANC) >0.5 × 10^9/L and first date of 3 consecutive laboratory values of platelet count >20 × 10^9/L without transfusion, respectively. The duration of hospitalization was defined as the total number of days that a patient stayed in a laminar airflow room. Duration of cytopenias was defined as the days when a patient's ANC was <1.0 × 10^9/L and platelet count was <100 × 10^9/L.

Stem cell mobilization and collection

Autologous Peripheral Blood Hematopoietic Stem Cells (PBHSCs) were utilized as grafts in all patients. Seventy six patients underwent PBHSCs mobilization with mobilization regimen of high-dose cyclophosphamide (at a dose of 50 mg/kg) plus subcutaneous Granulocyte Colony Stimulating Factor (G-CSF) at a dose of 10 μg/kg/day. Subsequently, patients underwent stem cell collection after an average of 7-9 days of G-CSF therapy. Apheresis was performed with the aim of collecting at least 4 × 10^6 CD34+cells/kg Ideal Body Weight (IBW). Minimum acceptable amount of hematopoietic stem cells was 2 × 10^6 CD34+cells/kg IBW. Reattempts were made in patients who failed to collect adequate amount of stem cells after the first procedure. Two patients failed to collect the minimum amount of PBHSCs required for autoHSCT following mobilization regimen of chemotherapy plus G-CSF, and were then remobilized by adding plerixafor to the regimen.

Treatment plan

In approximately 2-3 months from mobilization and collection of PBHSC patients were treated with HDC. Busulfan was administered intravenously at 0.8 mg/kg every 6 h on days -7, -6, and -5 (total dose 9.6 mg/kg) combined with etoposide 400 mg/m^2 IV over 7 hours on days -5 and -4 (total dose 800 mg/m^2) and cyclophosphamide 50 mg/kg IV over 2 hours on days -3 and -2 (total dose 100 mg/kg). Patients received mesna infusions to coincide with the cyclophosphamide infusions on days 3 and 2 at 0 h, 3 h, 6 h, and 9 h from the start of cyclophosphamide infusion for prevention of cyclophosphamide-induced hemorrhagic cystitis. Phenytoin sodium was given orally on the days of, and a day after busulfan infusion for seizure prophylaxis. Autologous PBHSCs were infused on day 0. Melphalan was administered intravenously at 100 mg/m^2/day over 1 h on days 3 and 2 (Total dose 200 mg/m^2). Four patients (1 patient had renal amyloidosis, 1 patient had myocardial amyloidosis, and 2 patients had multi-organ comorbidities) received melphalan 70 mg/m^2/day (total dose 140 mg/m^2). Patients were supplied with ice chips and cold water for oral hypothermia during melphalan infusion to prevent and mitigate mucositis. Autologous PBHSCs were infused on day 0.

Supportive care

All patients were housed in laminar airflow rooms, in a bone marrow transplant unit. Prophylactic alprostadil IV to prevent hepatic Veno-Occlussive Disease (VOD), ganciclovir IV to prevent cytomegalovirus disease, voriconazole, oral cotrimoxazole, piperacillin/tazobactam IV and esomeprazole/pantoprazole/lansoprazole were administered routinely from the beginning of conditioning therapy. Patients who suffered from neutropenic fever were treated with broad-spectrum antibiotics. For severe oral mucositis, low-level laser therapy and intravenous narcotic analgesics were administered as needed. The patient's urine pH was maintained at 6.8-7.5 by using an alkalinizing agent sodium bicarbonate solution with allopurinol and hydration of >2500-3000 ml/m^2/day of fluids. Recombinant human G-CSF and thrombopoietin were given from day +5 to stimulate hematopoietic recovery until the ANC and platelet count were >0.5 × 10^9/L and >20 × 10^9/L, respectively, for 2 consecutive days. Patients were transfused with irradiated blood products to maintain hematocrit >20% for symptomatic anemia and platelets >30 × 10^9/L.

Statistical analysis

The primary survival endpoints of the study were 1-year PFS and 1-year OS after a myeloablative conditioning regimen consisting of BVC *vs.* HDM. Secondary endpoints included cumulative incidence of relapse, transplantation-related mortality and toxicities. Survival was measured from the date of transplant. Descriptive statistics was used to report results including demographics, disease related factors, and transplant-related factors. Differences between groups were assessed using the T-test for continuous variables, and Chi-square

test for categorical variables to analyze and compare time to event outcomes. Categorical variables were summarized in frequency tables and cross-tabulations into percentages and proportions, and their corresponding P-values. Continuous variables were summarized into medians and ranges, and their corresponding P-values. Probabilities of PFS and OS were estimated using the Kaplan-Meier method and comparisons between groups were made with the Log-rank test. The probability of relapse (cumulative incidence of relapse) was generated using cumulative incidence data to accommodate the competing risk event, and comparison was made with the Gray test.

Multivariate analysis of relapse, PFS and OS were performed using Cox proportional hazards models which were used to estimate adjusted Hazard Ratios (HR) for BVC compared to HDM. The variables considered as multivariable were conditioning regimen, age, gender, KPS, MM subtype, disease stage, number of induction chemotherapy regimens, disease status at the time of transplantation, beta-2-microglobulin,time from diagnosis to transplantation and number of hematopoietic stem cells infused. All P-values shown are from two-sided tests, and the reported Confidence Intervals (CI) refer to 95% boundaries. The P-value of <0.05 was regarded as statistically significant in all analyses. SPSS software was used for data analyses. This study was conducted according to the ethical standards of Shandong University and was approved by the institutional review board of Qilu Hospital of Shandong University.

Results

Patient characteristics

General patient characteristics are summarized in Table 1. A difference in age between the patients who received the BVC conditioning (n=37, 47.4%) and those who received the HDM conditioning (n=41, 52.6%) was detected, with patients receiving HDM conditioning being significantly older (median: 53 years, range: 38-65) than those in the BVC group (median: 50 years, range: 29-63), P=0.002. Seventy three percent of patients in the BVC group and 61% of patients in the HDM group underwent autoHSCT within 12 months from diagnosis. Median follow-up for patients in the BVC group was 540 (7-1836) days, whereas median follow-up for patients in the HDM group was 436 (49-1316) days.

Engraftment and hospital stay

Data regarding patients' time in the laminar airflow rooms during treatment, duration of neutropenia, the number of transfusions as well as time to ANC and platelet engraftment are summarized in Table 2. Patients in the BVC group had significantly longer duration of hospitalization than patients in the HDM group (median: 20 days, range: 18-27) for BVC *vs.* median: 18 days, range: 13-27 for HDM; P<0.0001), most likely related to the difference in the number of days needed to administer drugs of the two regimens. The duration of cytopenia was significantly longer in the BVC group than in the HDM group (median: 7 days, range: 4-12 for BVC *vs.* median: 6 days, range: 2-12 for HDM; P=0.002). Likewise, more patients in the BVC group experienced febrile neutropenia (16(43.2%) patients) than in the HDM group (10(24.4%) patients), and had longer antibiotic administration time. However, the difference was not statistically significant, P=0.111 (Table 3). Median times to neutrophil and platelet engraftment were not significantly different between the two groups.

Regimen-related toxicity

Toxicities related to either of the conditioning regimens are summarized in Table 3. There were two cases of TRM, one in

Table 1: Characteristics of patients who underwent autologous stem cell transplantation with BVC or HDM.

Characteristics	BVC	HDM	P-value
Total number of patients	37 (47.4%)	41 (52.6%)	
Median follow-up, days (range)	540 (7-1836)	436 (49-1316)	0.088
Median age, years (range)	50 (29-63)	53 (38-65)	0.002*
Gender			0.337
Male	23 (62%)	21 (51%)	
Female	14 (38%)	20 (49%)	
Isotype			
IgG	20 (54%)	24 (58%)	
IgA	9 (24%)	8 (20%)	
IgD	2 (6%)	4 (10%)	
Others (LC/NS)	6 (16%)	5 (12%)	
ISS stage at diagnosis			0.499
I	17 (46%)	15 (37%)	
II	12 (32%)	16 (39%)	
III	8 (22%)	10 (24)	
Beta-2 microglobulin	2.04 (0.22-13)	2.35 (0.20-18.20)	0.631
KPS at transplant			0.851
≤ 80	4 (11%)	5 (12%)	
90 - 100	33 (89%)	36 (88%)	
Induction chemotherapy regimen			0.695
1	20 (54%)	20 (59%)	
>1	17 (46%)	14 (41%)	
$CD34^+$ cells infused (per kg)			0.185
$<2 \times 10^6$	0	3 (7%)	
$2\text{-}5 \times 10^6$	18 (49%)	21 (51%)	
$>5 \times 10^6$	19 (51%)	17 (42%)	
Time from diagnosis to transplant			0.268
<12 months	27 (73%)	25 (61%)	
>12 months	10 (27%)	16 (39%)	
Disease status at transplant			0.406
CR	26 (70%)	33 (80%)	
VGPR	4 (11%)	2 (5%)	
PR	7 (19%)	6 (15%)	

*Denotes statistically significant P-values (<0.05); IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgD: Immunoglobulin D; LC: Light Chain; NS: Non-secretory; ISS: International Staging System; KPS: Karnofsky Performance Status; CR: Complete Response; VGPR: Very Good Partial Response; PR: Partial Response

Table 2: Duration of hospitalization, duration of cytopenia, number of transfusions, and time to engraftment.

	BVC	HDM	P-value
Total number of patients	37	41	
Duration of hospitalization, days (range)	20 (18-27)	18 (13-27)	<0.0001*
Duration of cytopenia, days (range)	7 (4-12)	6 (2-12)	0.002*
Number of transfusions (range)	2 (1-4)	2 (1-8)	0.072
Median days to ANC engraftment (range)	10 (9-12)	10 (8-12)	0.395
Median days to platelet engraftment (range)	10 (8-17)	11 (9-15)	0.227

*Denotes statistically significant P-values (<0.05); ANC: Absolute Neutrophil Count

Table 3: Regimen-related toxicities.

Toxicity	BVC	HDM	P-value
Febrile neutropenia	16 (43.2%)	10 (24.4%)	0.111
Nausea/vomiting	30 (81.1%)	23 (56.1%)	n/s
Diarrhea	19 (51.3%)	19 (46.3%)	n/s
Mucositis	4 (10.8%)	8 (19.5%)	n/s
Pulmonary	2 (5.4%)	15 (36.6%)	0.002*
Cardiac	6 (16.2%)	4 (9.7%)	n/s
CNS	4(10.8%)	3 (7.3%)	n/s
Liver	1 (2.7%)	3 (7.3%)	n/s
Renal	1 (2.7%)	2 (4.9%)	n/s
Bladder	1 (2.7%)	0	n/s
TRM	1 (2.7%)	1 (2.4%)	n/s
No complications	2 (5.4%)	2 (4.9%)	n/s

*Denotes statistically significant P-values (<0.05); CNS: Central Nervous System; TRM: Transplantation-related Mortality; n/s: Non-Significant

each group. One patient in the HDM group developed severe gastrointestinal bleeding and acute cerebral infarction and died on day +38. A second patient in the BVC group died of sepsis caused by severe enterocolitis on day +23. There was statistically significant difference in the number of patients who developed pulmonary toxicities, including interstitial pneumonitis and pulmonary infections (bacterial and fungal) after transplant; 15 (36.6%) patients in the HDM group, while only 2 (5.4%) patients in the BVC group, P=0.002. Only one patient in the BVC group developed hemorrhagic cystitis after transplant despite preventive measures, but the condition was resolved with supportive care. Other toxicities presenting in less than 10% of the patients on both groups were neurological symptoms (hallucinations, irritability and insomnia), mild-moderate VOD with hyperbilirubinemia and ascites, and renal interstitial injury.

Outcomes and survival

Overall Response Rates (ORR) between both groups were similar; 75.7% of patients in the BVC group, including 20 (64.9%) patients achieved CR and 4 (10.8%) patients achieved PR, and 75.6% of patients in the HDM group, all achieved CR. These findings are summarized in Table 4. Progression-free survival was not significantly different between the two groups. As shown in Figure 1, the 1-year PFS for the BVC group was 68%, compared to 75% for the HDM group (P=0.589). The mean PFS was 34.6 months (95% CI: 26-43.2 months) in the BVC group, while the mean PFS in the HDM group was 30.9 months (95% CI: 24.9-36.9 months).The median PFS was 43 months (95% CI: 11.4-74.5 months) in the BVC group while the median PFS in the HDM group was not reached. The OS did not significantly differ between the two groups. The 1-year OS for the BVC group was 87%, while it was 93% for the HDM group (P=0.291), as shown in Figure 2. The mean OS was 50.1 months (95% CI: 41.6-58.6 months) in the BVC group, while the mean OS was 40 months (95% CI: 35.7-44.3 months) in the HDM group. The median OS for patients in both groups was not reached. Cumulative incidence of relapse at 1 year was 34.6% in the BVC group *vs.* 24.3% in the HDM group, but the difference was not statistically significant (P=0.434), as shown in Figure 3.

Table 4: Response status after autologous stem cell transplantation.

Response status	BVC	HDM
Complete response	24 (64.9%)	31 (75.6%)
Partial response	4 (10.8%)	0
Stable disease	3 (8.1%)	1 (2.4%)
Progressive disease	5 (13.5%)	8 (19.5%)
No response	1 (2.7%)	1 (2.4%)

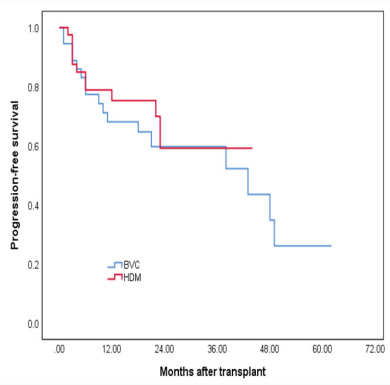

Figure 1: Kaplan-Meier curves of progression-free survival after autologous hematopoietic stem cell transplantation in patients receiving BVC *vs.* HDM (P=0.589).

Multivariable analysis of different subgroups; age, gender, disease stage, conditioning regimen, number of infused hematopoietic stem cells, MM isotypes, KPS, number of induction chemotherapy regimens, disease status before transplantation, or time of transplantation from diagnosis showed that only disease stage at diagnosis to be predictor of PFS and relapse risk; with patients in low-risk disease stages associated with longer time to progression; (ISS I: HR=0.186, 95% CI: 0.056-0.620; P=0.006 and ISS II: HR=0.240, 95% CI: 0.071-0.814; P=0.022), and delayed time to relapse; (ISS I: HR=0.220, 95% CI: 0.067-0.727; P=0.013 and ISS II: HR=0.262, 95% CI: 0.075-0.918; P=0.036), but did not predict OS. Beta-2-microglobulin was recognized as an independent prognostic factor of OS, with pretreated elevated levels of beta-2-microglobulin showed to significantly worsen the OS (HR=1.356, 95% CI: 1.013-1.815; P=0.041). No other patient or treatment characteristics were found to be statistically significant predictors of PFS, OS or relapse. In particular, the conditioning regimen was not associated with survival, indicating that BVC was not inferior to HDM with regards to PFS, OS and relapse risk.

Discussion

Multiple myeloma still remains incurable disease and most patients inevitably relapse and die of progressive disease [25]. While MEL200 is frequently used as the standard pre-transplantation conditioning regimen for MM patients aged ≤ 65 years [16] high rates of complete remission, the regimen is associated with high rates of morbidity and mortality. Many patients experienced disease progression or relapse after autoHSCT due to residual host tumor burden following HDC.

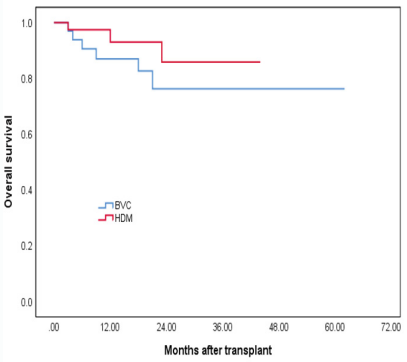

Figure 2: Kaplan-Meier curves of overall survival after autologous hematopoietic stem cell transplantation in patients receiving BVC *vs.* HDM (P=0.291).

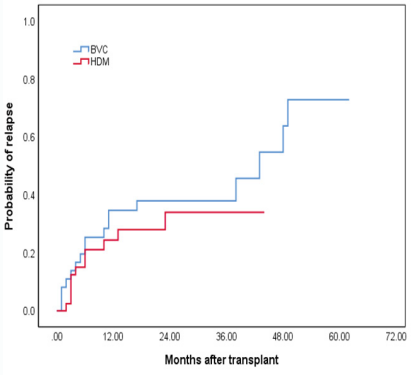

Figure 3: Kaplan-Meier curves of cumulative incidence of relapse after autologous hematopoietic stem cell transplantation in patients receiving BVC *vs.* HDM (P=0.434).

Hence, obtaining the maximum possible cytoreduction should be the target in order to improve the survival post-transplant. Previous studies have proposed BVC as an attractive alternative conditioning regimen to HDM prior to transplant and have been shown to be safe and effective [18], however, the regimen showed no superiority over HDM in terms of outcomes, survival or toxicity profiles [19-21].

In the present study, we summarize three institutions' experience of 78 total patients who received either BVC or HDM as conditioning regimen with autoHSCT as treatment for MM. Our findings, similar to the results of the previous studies [19,21], showed the BVC conditioning to be as effective as the HDM conditioning in terms of PFS,OS and risk of relapse, but differed in toxicity profiles. One of the key findings in this study is that there was significant difference between the two groups with regard to non-hematological toxicities, with more patients in the HDM group experienced pulmonary toxicities, than patients in the BVC group. However HDM conditioning was superior to BVC conditioning in terms of hematological toxicity (cytopenia). This was in contrast to the findings from Gu et al. [21], which showed that BVC conditioning produced equivalent outcomes with comparable non-hematological toxicities as HDM conditioning for patients with MM. Other two reports have shown comparable toxicity profiles between MM patients who were pretreated with either BVC or HDM conditioning before transplant [19,20]. To our knowledge, our study is the first to report the superiority of BVC conditioning to HDM in terms of pulmonary toxicity. In terms of drugs administration convenience and hospital stay, BVC conditioning was associated with significant longer hospital stay (an average of 2 days) than the length of hospital stay in the HDM group. This may be explained by a longer time needed to administer BVC drugs (6 days *vs.* 2 days needed to administer melphalan drug). Patterns of hematopoietic recovery was similar between the two groups in regard to neutrophil recovery, but patients in the HDM group took longer time for platelet recovery (an average of 1 day) and required more platelet transfusion than patients in the BVC group. But the differences did not reach statistical significance.

Another key finding in this study is that we found interaction of disease ISS I or ISS II with PFS or relapse, and interaction between beta-2-microglobulin and OS. The risks of disease progression or relapse significantly decreased in patients with low-risk stages (ISS stage I and II). As shown in a study by Aviles et al. [26], beta-2-microglobulin showed to predict OS, with the increasing levels of beta-2 microglobulin, the risk of death from the disease significantly increases. Given that the study is retrospective, major limitations to fully understand the predictors of the survival are the lack of availability of information regarding cytogenetics and serum C-Reactive Protein (CRP) levels for many patients. Hopefully with the emergence of novel agents, such as the IMiDs (thalidomide, lenalidomide and pomalidomide), PIs (bortezomib, carfilzomib and ixazomib) and monoclonal antibodies (daratumumab, isatuximab and elotuzumab) in treatment of MM, a more extensive exploration is needed to enhance the pre-transplantation conditioning regimen and improve the outcomes of MM patients undergoing autoHSCT.

Conclusion

Our study suggest BVC conditioning regimen may be an attractive alternative to HDM conditioning for newly diagnosed and relapsed MM patients undergoing autoHSCT. However, due to the retrospective nature of the study and a smaller sample size, preclude us from making definitive interpretation.

Acknowledgements

Funding

The present study was partially supported by the Clinical science and technology innovation program of Jinan science and technology project (201704085), and the Umbilical cord blood stem clinical application research project of Shandong Medical Association (YXH2019ZX007).

Authors' contributions

Xuebin Ji participated in developing study concept and study design. Lanhua Li assisted in developing study design, data collection and interpretation. Edith H. Kimambo developed study concept, managed data collection, analysis and interpretation, and drafted the manuscript. Yue Ling and Dongdong Ma managed data collection and interpretation. Wenjie Miao and Weifang Li assisted in data collection and interpretation. All authors provided critical review of the manuscript and approved the final version.

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