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ORIGINAL ARTICLE

Modified BuCy is an alternative conditioning regimen for lymphoma patients undergoing autologous stem cell transplantation

Haiwen Huang [1,2] · Lihong Zhang [1,2] · Yibin Jiang [1,2] · Shuo Liu [1,2] · Zhengming Jin [1,2] · Jia Chen [1,2] · Xiaofang Xiao [1,2] · Jia Ruan [1,2,3] · Xinyou Zhang [4] · Depei Wu [1,2]

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Abstract

The aim of this study is to determine whether the modified BuCy (semustine, cytarabine, busulfan, and cyclophosphamide, mBuCy) conditioning regimen can be safely used as an alternative to the SEAM (semustine, etoposide, cytarabine, and melphalan) regimen by comparing the efficacy and toxicity of the mBuCy and SEAM regimens. We matched 34 pairs of patients with regard to disease status at the time of autologous stem cell transplantation (auto-SCT). We found no significant difference in the time of platelet engraftment between the two groups. Furthermore, neutrophil engraftment was somewhat faster in the mBuCy group than in the SEAM group (median: 9 days vs 10 days, $p = 0.015$). With regard to toxicity, the incidence of nausea/vomiting, hepatic impairment, renal impairment, pulmonary infection, and treatment-related mortality (TRM) was similar between the two groups. In addition, compared to patients conditioned with SEAM, patients conditioned with mBuCy were less likely to develop mucositis and diarrhea ($p = 0.027$; $p = 0.050$). The 2-year progression-free survival (PFS) rates in the mBuCy and SEAM groups were 79% and 70% ($p = 0.378$), respectively, and the 2-year overall survival (OS) rates were 81% and 78.0%, respectively ($p = 0.789$). These analyses showed that the mBuCy conditioning regimen was well tolerated and can be used as an alternative to the SEAM regimen for lymphoma.

Keywords Modified BuCy · SEAM · High-dose chemotherapy · Lymphoma · Autologous stem cell transplantation

Introduction

In a subgroup of newly diagnosed and relapsed/refractory lymphomas, high-dose chemotherapy (HDC) followed by autologous stem cell transplantation (auto-SCT) is superior to conventional chemotherapy [1–3]. The most commonly used HDC regimen in lymphoma patients prior to auto-SCT is the BEAM (carmustine, etoposide, cytarabine, and melphalan) regimen [4–6], which is considered the "gold standard." However, the source of carmustine (BCNU) is restricted in China, which results in limited clinical application of the BEAM regimen. The busulfan-cyclophosphamide (BuCy) regimen is the most frequently used myeloablative conditioning regimen [7, 8], and a modified variant of BuCy (busulfan, cyclophosphamide, semustine and cytarabine, mBuCy) has been used as an alternative for myeloablative conditioning in acute myelocytic leukemia (AML) patients undergoing auto-SCT [9, 10]. Our center reported 75 AML patients undergoing auto-SCT with the mBuCy regimen between May 2007 and December 2013. This HDC regimen is well tolerated and efficacious [10]. Thus, we have also used mBuCy as a conditioning regimen

Haiwen Huang and Lihong Zhang are co-first authors.

✉ Haiwen Huang
huanghaiwen@suda.edu.cn

✉ Jia Ruan
jruan@med.cornell.edu

✉ Xinyou Zhang
zhangxinyou0518@sina.com

✉ Depei Wu
wudepei@medmail.com.cn

[1] Department of Hematology, The First Affiliated Hospital of Soochow University, No. 188. Shi Zi Street, Suzhou 215006, China

[2] Jiangsu Institute of Hematology, Key Laboratory of Thrombosis and Hemostasis of the Ministry of Health, Suzhou, Jiangsu, China

[3] Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York-Presbyterian Hospital, 1305 York Ave., 7th Fl, New York, NY, USA

[4] Department of Hematology, The Second Clinical Medical College (Shenzhen People's Hospital), Jinan University, No. 1017 Dongmen North Road, Shenzhen 518020, Guangdong, China

for lymphoma patients undergoing auto-SCT. However, whether this modified BuCy conditioning regimen can serve as an alternative to the BEAM regimen for lymphoma patients undergoing auto-SCT is still unclear due to a lack of relevant data. We substituted the SEAM (semustine, etoposide, cytarabine, and melphalan) conditioning regimen for the BEAM conditioning regimen as a control because carmustine and semustine (Me-CCNU), as nitrosourea derivatives, have been reported to exhibit qualitatively similar spectra of antitumor activity [11], clinical toxicity [12], kinetic effects on the hemopoietic system [13], metabolic disposition [14], and degradation and appear to act through similar degradation products [15, 16]. Hence, we conducted a retrospective study to compare the efficacy and toxicity of the mBuCy and SEAM regimens in lymphoma patients with a poor prognosis.

Patients and methods

Patients

From February 2014 to May 2018, a total of 101 Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) patients underwent HDC with the mBuCy ($n = 34$) or SEAM ($n = 67$) regimens followed by auto-SCT at our center. Patients with a poor prognosis at diagnosis or who had relapsed or refractory disease were eligible for auto-SCT. Patients were required to meet the following requirements before auto-SCT: age less than or equal to 65 years; adequate heart, lung, liver, kidney, and hematopoietic function; and an Eastern Cooperative Oncology Group (ECOG) performance score≤ 2. Many factors can affect the prognosis of auto-SCT, among which the disease status at the time of auto-SCT is one of the most important factors [17, 18]. We conducted a case matched-pair comparison to achieve a balance between the two sets of data. In our study, the two groups of patients were matched by the same disease status at the time of auto-SCT (ratio 1:1). Thirty-four pairs (68 patients) were included in the final analysis.

Mobilization of peripheral blood stem cells

Peripheral blood stem cells were mobilized in patients by granulocyte-colony stimulation factor (G-CSF; 10 μg/kg/day) alone ($n = 10$), disease-specific chemotherapy plus G-CSF ($n = 25$), cyclophosphamide (4 g/m^2) plus G-CSF ($n = 7$), or MAG (cytarabine, 2 g/m^2 q12 h d1-d2; mitoxantrone, 10 mg/m^2 d2-d3; G-CSF, 10 μg/kg/day) ($n = 26$). The optimal number of CD34-positive progenitor cells would be greater than 2×10^6/kg. For patients whose CD34-positive progenitor cells has not been reached 2×10^6/kg after repeated mobilization, hematopoietic stem cell transplantation will also be conducted if mononuclear cell count (MNC) is greater than 5×10^8/kg and the patient is really needed to be transplanted.

Conditioning regimens

The SEAM regimen consisted of Me-CCNU (250 mg/m^2/day, p.o.) on day − 8 (i.e., the 8th day before stem cell infusion), etoposide (100 mg/m^2, i.v.) every 12 h on days − 7 to − 4 (total dose 800 mg/m^2), cytarabine (200 mg/m^2, i.v.) every 12 h on days − 7 to − 4 (total dose 1600 mg/m^2), and melphalan (140 mg/m^2/day, i.v.) on day − 3 only. The mBuCy regimen consisted of Me-CCNU (250 mg/m^2/day, p.o.) on day − 10, hydroxyurea (40 mg/kg, p.o.) bid on day − 10 (total dose 80 mg/kg), cytarabine (2000 mg/m^2/day, i.v.) on days − 9 and − 8 (total dose 4000 mg/m^2), busulfan (0.8 mg/kg, i.v.) every 6 h on days − 7 to − 5 (total dose 9.6 mg/kg), and cyclophosphamide (1.8 g/m^2/day, i.v.) on days − 4 to − 3 (total dose 3.6 g/m^2). The administration schedule for all the regimens is detailed in Table 1.

Supportive care

All patients received G-CSF (5 μg/kg/day) subcutaneously from day 1 of auto-SCT until the absolute neutrophil count (ANC) was $> 1 \times 10^9$/L for three consecutive days. Washed red blood cells were given to maintain a hemoglobin level > 60 g/L. In addition, platelets were given to maintain the platelet count (PLTc) $> 20 \times 10^9$/L. Cotrimoxazole was used as prophylaxis against *Pneumocystis carinii*. Prophylaxis against fungi, bacteria, and viruses consisted of oral or intravenous triazole antifungals, oral norfloxacin, and intravenous ganciclovir, respectively. Administration of antimicrobial and antifungal agents to patients with febrile episodes was performed based on the individual condition of the patients. All patients positive for hepatitis B virus (HBV) infection were administered adefovir dipivoxil and/or entecavir to prevent HBV reactivation. Patients in the mBuCy group were given sodium valproate (800 mg) once daily starting the day before busulfan administration; sodium valproate was given for five consecutive days to prevent busulfan-associated seizures.

Response criteria and study definitions

After initial induction chemotherapy, salvage chemotherapy and HDC, the response to therapy was evaluated according to the International Workshop Criteria [19]. Neutrophil engraftment was defined as an ANC $\geq 0.5 \times 10^9$/L on the first of three consecutive days with no subsequent decline. Platelet engraftment was defined as a PLTc $\geq 20 \times 10^9$/L on the first of three consecutive days without the need for platelet transfusion. Treatment-related mortality (TRM) was defined as death from any cause other than disease relapse or progression occurring within the first 100 days after auto-SCT. Progression-free

Table 1 Conditioning regimens

Regimens	Drugs	Single dose	Usage	Total dose
mBuCy	Semustine	250 mg/m^2	D − 10, p.o.	250 mg/m^2
	Hydroxyurea	40 mg/kg	D − 10, p.o., bid	80 mg/kg
	Cytarabine	2000 mg/m^2	D − 9 to − 8, i.v.	4000 mg/m^2
	Busulfan	0.8 mg/kg	D − 7 to − 5, i.v., q6 h	9.6 mg/kg
	Cyclophosphamide	1.8 g/m^2	D − 4 to − 3, i.v.	3.6 g/m^2
SEAM	Semustine	250 mg/m^2	D − 8, p.o.	250 mg/m^2
	Etoposide	100 mg/m^2	D − 7 to − 4, i.v., q12 h	800 mg/m^2
	Cytarabine	200 mg/m^2	D − 7 to − 4, i.v., q12 h	1600 mg/m^2
	Melphalan	140 mg/m^2	D −3, i.v.	140 mg/m^2

survival (PFS) was measured from the time of transplantation to the time of disease relapse, disease progression, or death from any cause. Overall survival (OS) was measured from the time of auto-SCT to death from any cause or censored as of the date of the patient's last clinical follow-up evaluation.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Science (SPSS 19.0) software. Categorical variables were compared using Fisher's exact test, and continuous variables were compared using the Mann-Whitney *U* test. PFS and OS were compared with the log-rank test and plotted using the Kaplan-Meier method. All *p*-values were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

The characteristics of patients receiving the mBuCy ($n = 34$) or SEAM ($n = 34$) regimen are listed in Table 2. The median age at transplantation was 39 (13–61) years in the mBuCy group and 39 (15–65) years in the SEAM group ($p = 0.787$). No statistically significant differences were found between the groups in terms of gender, histological types of lymphoma, International Prognostic Index (IPI) at diagnosis, ECOG score, Ann Arbor stage, bone marrow involvement, level of serum lactate dehydrogenase (LDH) at transplantation, radiotherapy prior to transplantation, and the number of chemotherapy regimens undergone prior to transplantation.

Hematopoietic engraftment

One patient in the SEAM group died on day + 8 (i.e., the 8th day after stem cell infusion) and was not evaluated for engraftment. Therefore, we evaluated 63 patients for hematopoietic engraftment, the outcomes of which are shown in Table 3. The time to neutrophil engraftment was shorter ($p = 0.015$) in the mBuCy group than in the SEAM group, with medians of 9 days (range, 8–12 days) and 10 days (range, 8–14 days) respectively. The median time to platelet engraftment was 11 days (range, 7–30 days) in the mBuCy group and 12 days (range, 9–30 days) in the SEAM group ($p = 0.647$).

Toxicity and treatment-related mortality

All treatment-related toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. Non-hematological treatment-related toxicities are shown in Table 4. Patients receiving the mBuCy regimen had less severe mucositis and diarrhea than patients receiving the SEAM regimen (91.2% vs 97.1%, $p = 0.027$; 64.7% vs 82.4%, $p = 0.050$). No statistically significant differences in other non-hematological treatment-related toxicities were observed between the two groups. Febrile neutropenia occurred in 55.9% and 64.7% of patients conditioned with mBuCy and SEAM regimens, respectively ($p = 0.457$). Of these patients, one patient in the mBuCy group and two patients in the SEAM group had positive blood cultures. They all received appropriate antibiotic therapy, but one patient in the SEAM group died of progressive sepsis on day + 8. Three of the SEAM patients had mild gastrointestinal bleeding. Hepatotoxicity (i.e., elevated liver enzymes and/or bilirubin) occurred in 15 patients (11 grade I, 4 grade II) in the mBuCy group and 12 patients (7 grade I, 4 grade II, 1 grade III) in the SEAM group, but no patient developed hepatic veno-occlusive disease (VOD). Two patients in the mBuCy group and three patients in the SEAM group experienced mild renal impairment. Seizures occurred in two patients in the mBuCy group. In addition, these patients did not experience seizure again after therapeutic doses of sodium valproate and phenobarbital were given. The only cases of TRM resulted from pneumonia in one patient in the SEAM group, who died on day + 8, and a patient in the mBuCy group, who died on day + 90 after transplantation.

Table 2 Patient characteristics

	mBuCy ($n = 34$)	SEAM ($n = 34$)	p value
Median age at transplantation (range)	39 (13–61)	39 (15–65)	0.787
Gender, *n* (%)			0.808
Male	18 (52.9%)	17 (50.0%)	
Female	16 (47.1%)	17 (50.0%)	
IPI at diagnosis			0.636
0–1	12 (35.3%)	10 (29.4%)	
2	17 (50.0%)	16 (47.1%)	
3	5 (14.7%)	8 (23.5%)	
ECOG, *n* (%)			1.000
0	2 (5.9%)	2 (5.9%)	
1	32 (94.1%)	32 (94.1%)	
Histological subtype, *n* (%)			0.919
HL	4 (11.8%)	5 (14.7%)	
BCL	21 (61.8%)	21 (61.8%)	
T/NK CL	9 (26.5%)	8 (23.5%)	
Ann Arbor stage, *n* (%)			0.770
I–II	7 (20.6%)	8 (23.5%)	
III–IV	27 (79.4%)	26 (76.5%)	
Bone marrow involvement, *n* (%)	5 (14.7%)	5 (14.7%)	1.000
LDH at transplantation, *n* (%)			
Normal	22 (64.7%)	20 (58.8%)	0.618
Above normal	12 (35.3%)	14 (41.2%)	
Number of chemotherapy regimens prior to transplantation, *n* (%)			0.869
1	12 (35.3%)	10 (29.5%)	
2	15 (44.1%)	16 (47.1%)	
≥ 3	7 (20.6%)	8 (23.5%)	
Radiotherapy prior to transplantation, *n* (%)			0.555
	1 (2.9%)	2 (5.9%)	
Disease status at transplantation, *n* (%)			
CR	17 (50.0%)	17 (50.0%)	1.000
PR	13 (38.2%)	13 (38.2%)	
SD	1 (2.9%)	1 (2.9%)	
PD	3 (8.8%)	3 (8.8%)	

(*IPI*, International Prognostic Index; *ECOG*, Eastern Cooperative Oncology Group; *HL*, Hodgkin's lymphoma; *BCL*, B-cell non-Hodgkin's lymphoma; *T/NK CL*, T/NK-cell non-Hodgkin's lymphoma; *LDH*, lactate dehydrogenase; *CR*, complete remission; *PR*, partial remission; *SD*, stable disease; *PD*, progressive disease)

Table 3 Hematopoietic engraftment after auto-SCT

	mBuCy ($n = 34$)	SEAM ($n = 34$)	p value
Number of infused $CD34^+$ cells ($\times 10^6$/kg)	5.26 (1.29–23.24)	4.26 (0.613–28.86)	0.244
Transfused RBC (units)	0 (0–7.5)	0 (0–6)	0.873
Transfused PLT (units)	3 (1–12)	3 (1–13)	0.068
Time to ANC $\geq 0.5 \times 10^9$/L (days)	9 (8–12)	10 (8–14)	0.015*
Time to PLTc $\geq 20 \times 10^9$/L (days)	11 (7–30)	12 (9–30)	0.647
Hospitalization duration (days)	27.5 (21–43)	26 (21–39)	0.267

RBC, red blood cell; *ANC*, absolute neutrophil count; *PLTc*, platelet count

* Statistically significant

Table 4 Toxicity and response to auto-SCT

	mBuCy ($n = 34$)	SEAM ($n = 34$)	p value
Nausea/vomiting, *n* (%)			0.313
Grades I–II	24 (70.6%)	21 (61.8%)	
Grades III–IV	4 (11.8%)	7 (20.6%)	
Mucositis, *n* (%)			0.027*
Grades I–II	29 (85.3%)	24 (70.6%)	
Grades III–IV	2 (5.9%)	9 (26.5%)	
Diarrhea, *n* (%)			0.050*
Grades I–II	21 (61.8%)	21 (61.8%)	
Grades III–IV	1 (2.9%)	7 (20.6%)	
TRM, *n* (%)	1 (2.9%)	1 (2.9%)	1.000
FN, *n* (%)	19 (55.9%)	22 (64.7%)	0.457
Gastrointestinal bleeding, *n* (%)	0 (0%)	3 (8.8%)	0.076
Pulmonary infection, *n* (%)	4 (11.8%)	5 (14.7%)	0.720
Hepatic impairment, *n* (%)	15 (44.1%)	12 (35.3%)	0.121
Renal impairment, *n* (%)	2 (5.9%)	3 (8.8%)	0.642
Septicemia, *n* (%)	1 (2.9%)	2 (5.9%)	0.555
Response to ASCT, *n* (%)			0.897
CR	22 (64.7%)	21 (61.8%)	
PR	8 (23.5%)	7 (20.6)	
SD	0 (0%)	0 (0%)	
PD	3 (8.8%)	4 (11.8%)	
Unknown	0 (0%)	1 (2.9%)	

(*TRM*, treatment-related mortality; FN, febrile neutropenia; *CR*, complete remission; *PR*, partial remission; *SD*, stable disease; *PD*, progressive disease

* Statistically significant

Response and survival

Sixty-five patients (mBuCy, 33 patients; SEAM, 32 patients) were evaluable for treatment response at 3 months after hematopoietic stem cell transplantation. Twenty-two patients (64.7%) in the mBuCy group and 21 patients (61.8%) in the SEAM group achieved complete remission ($p = 0.897$, Table 4). However, three patients in the mBuCy group and four patients in the SEAM group suffered progressive disease within this 3-month interval. Finally, two

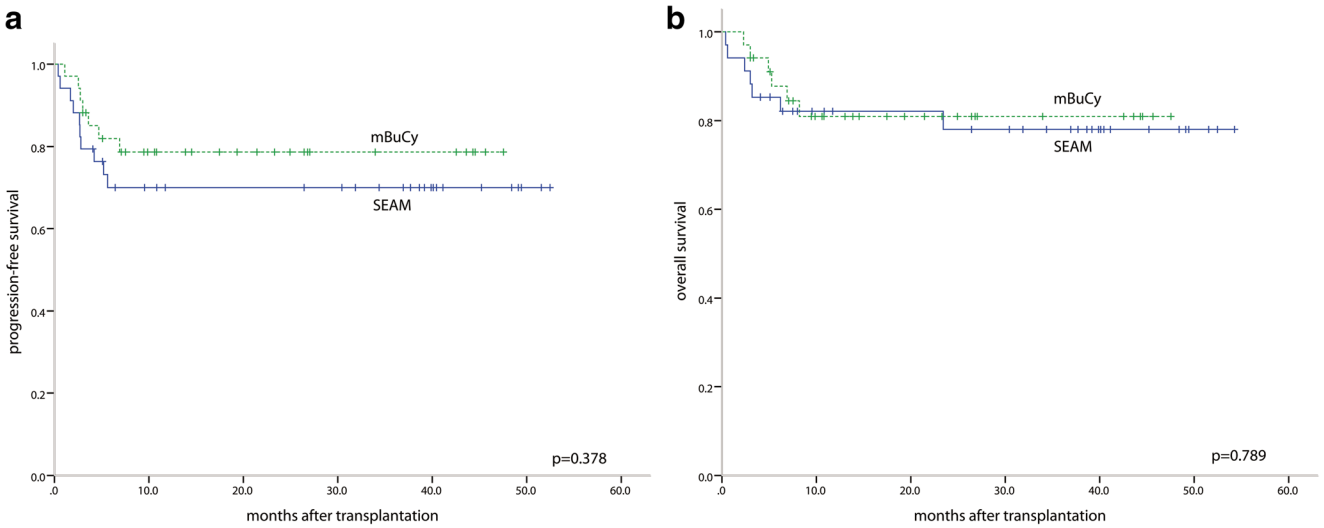

Fig. 1 Comparison of outcomes after HDC with mBuCy or SEAM, followed by autologous stem cell transplantation. **a** Progression-free survival. **b** Overall survival

patients in each group did not achieve remission after receiving salvage therapy and died of disease progression, and one patient in the mBuCy group and two patients in the SEAM group were undergoing salvage chemotherapy at the end of the follow-up period. With a median follow-up of 19.3 months (range, 3.0–47.5 months) in the mBuCy group and 39.9 months (range, 4.0–54.3 months) in the SEAM group, neither the median OS nor median PFS was reached in either group. The estimated 2-year PFS was 79.0% in the mBuCy group and 70.0% in the SEAM group ($p = 0.378$, Fig. 1a). In addition, the estimated 2-year OS was 81.0% in the mBuCy group and 78.0% in the SEAM group ($p = 0.789$, Fig. 1b).

Discussion

Conditioning regimen-related toxicity is an important cause of both early and long-term mortality after transplantation. An ideal conditioning regimen should show not only high anti-tumor activity but also acceptable and manageable toxicity, which is the key to the success of auto-SCT. The BEAM regimen is the most widely used conditioning regimen because of its apparent tolerability and established efficacy [5, 20, 21]. However, clinical application of the BEAM regimen is restricted in China. We substituted Me-CCNU for BCNU to produce the SEAM conditioning regimen, which was used in the control group. By comparing the efficacy and toxicity of the mBuCy and SEAM regimens, we showed that the mBuCy conditioning regimen was well tolerated and can be an alternative to the SEAM regimen.

Reports of busulfan and cyclophosphamide combined with cytarabine and Me-CCNU as a conditioning regimen for auto-SCT are more common for AML. The safety and efficacy of this mBuCy regimen has previously been demonstrated in AML auto-SCT [9, 10]; however, there is no information on the toxicity and efficacy of mBuCy in autologous transplantation for lymphoma. Only a few studies have compared the efficacy and toxicity of the BuCyE (busulfan, cyclophosphamide, and etoposide) and BEAM conditioning regimens in autologous transplantation for lymphoma. A study by Berber et al. [22] found that hematologic recovery and survival outcomes were similar in the BEAM and BuCyE groups. However, Kim et al. [23] reported that the hematologic recovery was significantly faster in the BuCyE group than in the BEAM group. In addition, the OS and event-free survival (EFS) did not differ significantly between the two groups. From these data, it appears that we can conclude that BuCy-containing conditioning regimens are not inferior to the BEAM conditioning regimen in supporting hematopoietic reconstruction and promoting survival outcomes. Similarly, we found that the neutrophil engraftment time was more rapid after mBuCy and that the platelet engraftment time was not significantly different between the mBuCy and SEAM groups. This may be partly due to the increased myelotoxicity of the SEAM regimen. Meanwhile, we found no statistically significant differences between the groups in terms of OS and PFS, suggesting that the mBuCy regimen is as effective as the SEAM regimen in autologous transplantation for lymphoma.

An optimal conditioning regimen is well tolerated with acceptable toxicity. Our analysis suggested that the mBuCy group had fewer non-hematological treatment-related toxicities, such as mucositis and diarrhea, than the SEAM group. Other non-hematological treatment-related toxicities, such as pulmonary infection and hepatic and renal impairment, were similar in the two groups. The higher incidence of diarrhea and mucositis in the SEAM group can likely be attributed to the inclusion of melphalan, which is well known to cause intestinal mucositis, sometimes at a severe level [24]. Serious mucositis may cause mucosal epithelial damage and submucosal vascular destruction, increasing the risk of infection and gastrointestinal bleeding. In our study, mild gastrointestinal bleeding occurred in three patients in the SEAM group, which may be explained by such intestinal mucositis.

Prior studies reported that busulfan is a chemotherapeutic agent associated with hepatic VOD [25, 26], which is the most serious and potentially life-threatening complication of a Bu-based regimen. In our study, however, hepatic VOD was not observed in either group. Two reasons for this outcome are as follows: (1) the use of i.v. busulfan; Ulrickson et al. [27] reported that patients receiving oral busulfan were more likely to develop hepatic VOD than those receiving i.v. busulfan and (2) the improvement of supportive care; with the development of the economy and advances in medicine, supportive care is further improved. The incidence of hepatic VOD and other life-threatening complications has been significantly reduced. TRM also has decreased in recent years due to improvements in supportive care. Our study found that the TRM of the two regimens was approximately 3%, which was lower than previously reported [28, 29].

Although the groups were similar with regard to patient characteristics and the median numbers of peripheral hematopoietic stem cells, our study still has several limitations, including its retrospective nature, the small sample size, and the shorter follow-up time of the mBuCy group. A prospective randomized trial with an adequate number of patients should be conducted to determine whether one of these regimens is superior to the other.

In summary, the mBuCy conditioning regimen was found to be well tolerated with acceptable non-hematological toxicity. Patients who underwent auto-SCT after mBuCy had similar survival outcomes and faster neutrophil engraftment than a matched pair cohort who underwent auto-SCT after SEAM, indicating that the mBuCy regimen can be considered a valid alternative to SEAM for lymphoma patients.

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Compliance with ethical standards

This study was conducted in compliance with the institutional policy regarding the protection of patients' private information and approved by the Research Ethics Committee of the First Affiliated Hospital of Soochow University. All the methods were carried out in accordance with the approval guidelines of The First Affiliated Hospital of Soochow University.

Conflict of interest The authors declare that they have no conflict of interest.

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