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Modified Conditioning Regimen MCE in Upfront HSCT Provides a Substantial Survival Benefit in High-risk DLBCL

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Abstract

Background: High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT) remains controversial as a front-line therapy for high-risk diffuse large B cell lymphoma (DLBCL). Moreover, whether modifying the conditioning regimen with anthracyclines for DLBCL will improve the effect and achieve a deeper response in upfront HSCT remains unexplored.

Methods: In the present study, we retrospectively compared the outcomes of 156 high-risk DLBCL patients treated with non-HSCT, upfront HSCT or salvage HSCT with a conditioning regimen consisting of mitoxantrone, etoposide, and cyclophosphamide (MCE).

Result: We found that an MCE conditioning regimen achieved a complete hematopoietic engraftment and well-tolerated, the incidence of grade 1–2 cardiac toxicity was 3.1%. Transplant-related mortality did not occur. The overall survival (OS) and progression-free survival (PFS) of the upfront group (117.8 and 92.9 months) were substantially longer than that of the non-HSCT group (78.1 and 48.9 months) (P = 0.001 vs P = 0.009), also much longer than that of salvage HSCT group (58.3 m and 21.5 m) (P = 0.00 vs P = 0.00). The multivariate analysis that AnnArbor Stage was related to PFS and OS in upfront HSCT with the MCE regimen.

Conclusions: The upfront HSCT with MCE regimen was well-tolerated and exhibited intriguing data in front line therapy to improve the high-risk DLBCL prognosis. However, whether high-risk DLBCL should receive consolidation HSCT with an MCE regimen after an initial CR requires a prospective, large-scale, long-term clinical trials to validate.

Retrospectively registered: This study was approved by the Ethical Committee of Huadong Hospital with the Ethical number of 2021K126.

Background

Diffuse large B cell lymphoma (DLBCL) is the most common form of aggressive lymphoma. Although the majority of patients with DLBCL achieve complete remission (CR), approximately 40% die from the disease [1]. The patient prognosis was classified as high or high-intermediate (higher) risk by international prognostic index (IPI) is extremely poor, primarily due to the high relapse rate. This suggests that minimal residual tumor that is not detected in the clinical CR state induces relapse. To improve the prognosis of higher risk patients, undetectable residual tumor in the first CR (CR1) state should be removed to prohibit relapse. High-dose chemotherapy (HDC) represents a standard front-line therapy for patients with aggressive non-Hodgkin lymphoma (NHL) for decades. Autologous hematopoietic stem cell transplantation (ASCT) is the standard of care (SOC) for relapsed/refractory DLBCL [2–4]. ASCT can eliminate the residual tumor cells, thereby decreasing the probability of disease recurrence and prolonging patient survival [5]. In an effort to improve the suboptimal outcomes of patients with aggressive NHL with intermediate-high or high aaIPI, postinduction therapy intensification with high-dose therapy and autologous hematopoietic stem cell transplantation (auto-HCT) has been investigated.

Several randomized trials in the pre-rituximab era have evaluated the role of auto-HCT consolidation in patients with aggressive NHL in their first remission[6–8]. A meta-analyses of these pre-rituximab era randomized trials have not demonstrated any survival benefit for auto-HCT in this setting [9, 10]. There were four randomized clinical trials (RCTs) during the rituximab era that evaluated the role of upfront auto-HCT consolidation in patients with DLBCL in a first remission with conflicting results [11–14].

While conditioning regimens in traditional auto-HSCT were frequently BuCyE (busulfan, cyclophosphamide, and etoposide) [15, 16] and Benda-EAM (bendamustine, etoposide, cytarabine, and melphalan) [17, 18], which were approved to be effective and safe for NHL patients. Anthracycline drugs were important and effective for DLBCL induction therapy to reduce the tumor burden, whereas anthracycline drugs were rarely reported to be added to the conditioning regimen. In 1997, Engert et al. found that IIVP (ifosfamide, idarubicin, and etoposide) was a salvage regimen with acceptable toxicity and highly effective for patients with R/R NHL [19]. The study by Tian et al. retrospectively compared the outcomes of 72 aggressive B cell NHL patients treated with IEAC (containing idarubicin) or BEAC regimens followed by ASCT as an upfront consolidative treatment. The IEAC regimen was well-tolerated, whereas the overall survival (OS) and progression-free survival (PFS) of IEAC group (33 and 23 months) were moderately longer than that of the BEAC group (30 and 18 months) [20]. Together, these findings indicate that the appropriate modification of the conditioning regimen in auto-HSCT might further improve the efficiency of HSCT. Moreover, the addition of anthracycline drugs in the condition regimen might further improve the treatment response and prognosis of DLBCL, especially intermediate to high risk DLBCL, and might even improve the prognosis of upfront HSCT patients compared to non-HSCT patients in intermediate to high risk DLBCL.

We retrospectively collected the data of high risk DLBCL patients from our center and these data were sub-divided into the following three groups: 1) DLBCL without HSCT; 2) DLBCL with upfront HSCT (after the first complete remission); and 3) DLBCL with salvage HSCT. The conditioning regimen for DLBCL at our center consists of mitoxantrone (an anthracycline drug), etoposide, and cyclophosphamide. We evaluated the safety and efficacy of this therapy and clarified its applicability. In addition, we compared the survival data of patients with upfront HSCT with non-HSCT patients, as well as salvage HSCT patients to evaluate whether high risk DLBCL patients could obtain a survival benefit from auto-HSCT following the first complete remission.

Patients And Methods

Patients

Patients were enrolled from January 2013 to December 2020 from the Department of Hematology, Huadong Hospital (Shanghai, China). We collected 156 patients from our center, all of whom were diagnosed with diffuse large B cell lymphoma, with Stage III or IV, IPI score ≥ 4, or IPI = 3 with a high risk molecular characteristics (e.g., ABC subtype, double or triple expression of BCL-2, BCL-6 or c-myc, or Bcl2 re-arrangement, or Bcl6 re-arrangement, or c-myc re-arrangement). The patients had no vital organ

dysfunctions and liver, kidney, and heart functionality was normal or nearly normal. This study was approved by the Ethical Committee of Huadong Hospital with the Ethical number of 2021K126.

Treatment

We enrolled 156 patients at our center. All of these patients had a diagnosis of diffuse large B cell lymphoma, with a Stage III or IV, IPI score = 3, with a high-risk molecular characteristic (e.g., ABC subtype, double or triple expression of BCL-2, BCL-6 or c-myc, or *Bcl-2* re-arrangement, *Bcl-6* re-arrangement, or *c-myc* re-arrangement), or IPI ≥ 4. All patients received 4–6 cycles of standard chemotherapy (e.g., R-CHOP [doxorubicin 50 mg/m^2]) regimen and 18-fuorodeoxyglucose positron emission tomography/computed tomography (PET-CT) was performed to evaluate the remission status before and after ASCT. A flow diagram of the treatment used in this study is shown in Fig. 1.

Whether these patients require upfront auto-HSCT remains controversial. Several clinical trials have provided conflicting results, while the conditioning regimen in these trials primarily consisted of BEAM. All DLBCL patients at our center received HSCT with a conditioning regimen of high dose mitoxantrone, etoposide, and cyclophosphamide. A total of 91 patients at our center with intermediate to high risk DLBCL did not receive auto-HSCT after the first complete remission, 55 high risk DLBCL patients at our center received upfront auto-HSCT after the first complete remission, and 10 patients received salvage auto-HSCT after disease relapse or recurrence and obtaining a second CR or PR. We used acyclovir, SMZ, and moxifoxacin as supportive care during HSCT. No patients received consolidation radiation therapy following transplantation. Patients received non-HSCT, front-line HSCT, or salvage HSCT depending on the patient age, physical status, disease status, and willingness. If high risk DLBCL patients were younger than 65 years old and achieved a CR or PR, they were eligible to receive auto-HSCT. If they agreed, they would be enrolled into the upfront HSCT group and receive HSCT. If they refused to receive HSCT, they could be enrolled in the non-HSCT and undergo observation. If the patients had undergone relapse, and achieved a second CR, there were eligible to receive auto-HSCT. If they agreed, they were enrolled into the salvage HSCT group and received HSCT.

Mobilization and collection of blood grafts

All the patients received chemo-mobilization (CTX 30 mg/kg + VP-16 15 mg/kg) according to institutional standards of care. G-CSF mobilization was administered to patients during the beginning of myelo-suppression recovery, in which 5 μg/kg G-CSF was administered daily for 6 days. Apheresis was initiated from the fifth day and continued daily for 2 days until the predetermined minimal target yield (mononuclear cells ≥ 2.0×10^8/kg and CD34$^+$ cells ≥ 1.0×10^6 /kg) was achieved. Blood grafts were successfully collected from all patients without plerixafor (PLER). Apheresis was initially performed using a Spectra AutoPBSC (Terumo BCT, Lakewood, Colorado) apheresis machine. The circulating blood volume was two to three times that of the patients' estimated total blood volume. The number of CD34$^+$ cells in each apheresis bag was measured by flow cytometry using the International Society of Hemotherapy and Graft Engineering protocol with a single platform method at the stem cell laboratory of each apheresis center.

Graft analysis

Two 0.5-mL specimens were collected from each apheresis bag for flow cytometry to evaluate both the $CD34^+$ and lymphocyte subclasses. The samples were immediately analyzed to distinguish graft cellular composition with flow cytometry (FACSCanto, Beckman) by a single experienced flow cytometrist (A.R.) at the Department of Hematology, Huadong Hospital, Fudan University. Antibodies against the following cell surface markers were used: CD34, CD38, CD133, and CD45. All of the antibodies were provided by Beckman Coulter. The absolute number of T, B, and NK cells, as well as the $CD3^+CD4^+$ and $CD3^+CD8^+$ T cell subpopulations in the grafts were determined using CD3/CD8/CD45/CD4 and CD3/CD16 + CD56/CD45/CD19 markers.

High-dose therapy and post-transplant course

MAC (mitoxantrone 60 mg/m^2 on d-1, etoposide 30 mg/kg on d-1, cyclophosphamide 60 mg/kg on d- 1) was used as a high-dose therapy (HDT) for DLBCL patients. The graft was infused on Day 0 without freezing. Filgrastim was administered after the graft infusion. Neutrophil engraftment was defined as the days to achieve a neutrophil count > 0.5×10^9 /L after graft infusion. Platelet (PLT) engraftment following graft infusion was defined as a PLT count > 20×10^9 /L for the previous three consecutive days without PLT transfusions. Hematopoietic recovery was analyzed by measuring the complete blood counts at Day + 15 and at 1, 3, 6, and 12 months. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria, version 4.0.

Endpoint and follow-up

According to the 2016 NCCN recommended LUGANO evaluation criteria, the efficacy evaluation was divided into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) was defined as the proportion of CR and PR. All patients were evaluated by positron emission tomography computed tomography (PET/CT) examination of the entire body before auto-HSCT or after chemotherapy had ended. After the end of chemotherapy or auto-HSCT, the enrolled patients were regularly followed up every three months during the first year, every six months during the second year, and once per year in the third year. All of the patients received a whole blood test, as well as a whole body CT scan and cardiac ultrasound. Progression free survival (PFS) was defined as the time from the first evaluation of efficacy as CR or PR to the first evaluation of PD or death from any cause.

The follow-up for this study ended on December 30, 2021. The data was recorded based on the last hospitalization record, out-patient review, and telephone follow-up. The overall survival (OS) time was defined as the time from the start of randomization to the date of death of the patient due to any cause or the date of the last follow-up. The PFS time was defined as the time from randomization to the date of disease progression or death or last patient follow-up. In this study, OS and PFS were calculated on a monthly basis.

Statistical analysis

The patient characteristics were summarized according to the mean and standard deviation for numerical valued variables and frequencies with percentages for categorical variables. Differences in the patient characteristics between the two groups were assessed using a Student's *t*-test for numerical variables and a Fishers' exact test for categorical variables. F-tests and Chi-square tests were used to assess. The Kaplan-Meier (KM) method was used to estimate the unadjusted probabilities of the OS and PFS time. The unadjusted OS and PFS between subgroups were compared with a Log-rank test. The joint effects and prognostic factors of the patient covariates and treatment arms for the OS and PFS were assessed with Cox regression models. SPSS 20.0 software was used to perform all frequent statistical analyses. $P < 0.05$ was considered to be statistically significant.

Results

Clinical characteristics

The patients' clinical characteristics were shown in Table 1. Of the 156 high risk DLBCL patients in the retrospective cohort, they could be divided into three groups: 1) the non-HSCT group, in which 91 patients only received conventional chemotherapy. After six cycles of conventional chemotherapy and two cycles of rituximab treatment, the patients could achieve CR/PR. Every three cycles, we would evaluate the disease situation without additional treatment; 2) the upfront HSCT group, in which there were 55 patients received conventional chemotherapy. After an evaluation of the disease situation and achievement of CR/PR following six cycles of chemotherapy, the patients received auto-HSCT with the MCE regimen (i.e., mitoxantrone, cyclophosphamide, and etoposide); and 3) the salvage HSCT group, in which 10 patients received six cycles of conventional chemotherapy and two cycles of rituximab treatment. After evaluation, they could achieve CR or PR, followed by stop treatment and follow up. If disease recurrence occurred, the patients received induction chemotherapy again. If they could achieve CR/PR again and were eligible for auto-HSCT, they would receive auto-HSCT (Fig. 1). The clinical characteristics between the three groups (e.g., gender, age, IPI score, Ann Arbor stage, LDH level, GCB subtype, molecular genetics, Ki67, and B syndrome) did not exhibit any significant difference (Table 1). A total of 69 out of 91 patients in the non-HSCT group received CR stage after six cycles of chemotherapy, 42 out of 55 patients in the upfront HSCT group received CR stage after six cycles of chemotherapy and prior to HSCT, 7 out of 10 patients in the salvage HSCT group received the CR stage before HSCT. No significant differences existed between the three groups ($P = 0.549$, Table 1)

Table 1
Clinical Characteristics of high risk DLBCL patients in the non-HSCT, upfront HSCT, and the Salvage HSCT groups

	Chemotherapy (n = 91)	Upfront HSCT (n = 55)	Salvage HSCT (n = 10)	*P* value
Gender(Male/Female)	53/38	33/22	7/3	0.77
Age	54.2(51.5–60)	48.9(45.8–52.0)	46.5(35.6–57.4)	0.16
IPI Score (3/4–5)	36/55	22/33	3/7	0.829
Ann Arbor (III or IV/II)	77/14	52/3	10/0	0.091
LDH (below 250U/L)/above 250U/L	45/46	34/21	5/5	0.337
GCB/non-GCB	17/74	6/49	3/7	0.239
Double Expression	26/91	20/55	3/10	0.844
Triple Expression	8/91	6/55	1/10	0.844
Double hit	4/91	5/55	1/10	0.475
Ki67	67.8(63.8–72.8)	73.6(69.5–77.7)	65.9(48.0–90)	0.191
B syndrome	42/91	35/55	6/10	0.11
BM involvement	18/91	24/55	4/10	0.07
CR/PR	69/22	42/13	7/3	0.549

Hematopoietic engraftment

All patients achieved a complete hematopoietic engraftment. The median time to neutrophil engraftment (> 500/mm^3) was 14.5 (9.4 − 19.6) d, the median time to platelet > 20000 × 10^3/mm^3 engraftment was 16.8 (7.9 − 25.7) d. The median Platelet infusion was 1.1 (0.8 − 1.2) unit, and the median RBC infusion was 1.4 (1.2 − 1.5) unit. The collected total MNC count was 1.94 (1.01 − 2.73) × 10^8 /Kg, the collected CD34 + count was 1.09 (0.2 − 2.01) × 10^6 /Kg (Table 3).

Table 2
Relapse and Survival data of the upfront auto-HSCT with an MCE regimen, Salvage HSCT, and non-HSCT groups

	Chemotherapy (n = 91)	Upfront HSCT (n = 55)	Salvage HSCT (n = 10)	*P* value
100d non-relapse mortality after HSCT	0/91(0%)	1/55(1.8%)	1/10(10%)	0.049
1-y relapse rate	14/91(15.4%)	1/55(1.8%)	3/10(30%)	0.005
2-y relapse rate	22/91(24.2%)	4/55(7.3%)	7/10(70%)	0.000
3-y OS	85%	98%	70%	0.000
3-y PFS	60.2%	91.8%	22.2%	0.000
5-y OS	75.5%	98%	46.2%	0.000
5-y PFS	43.6%	88.3%	0	0.000

Table 3
Hematological Engraftment of the MCE regimen

	N
Time to neutrophil > 500×10^3/mm^3	14.5(9.4–19.6) d
Time to platelet > 20000×10^3/mm^3	16.8(7.9–25.7) d
Platelet infusion	1.1(0.8–1.2)
RBC infusion	1.4(1.2–1.5)
MNC count	1.94(1.01–2.73)×10^8 /Kg
CD34 + count	1.09(0.2–2.01)×10^6 /Kg

Adverse events

The toxicity of the MCE (mitoxantrone, cyclophosphamide, and etoposide) conditioning regimen is shown in Table 4. We collected the toxicity to day + 30. The most common related adverse events (AEs) observed in all patients consisted of febrile neutropenia (grade 4, 100%), nausea and vomiting (grade 3–4, 80%), oral mucositis (grade 3–4, 7.7%), cardiac toxicity (grade 1–2, 3.1%), veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS, 0%), and central nervous system (CNS) adverse reactions (grade 1–2, 7.7%). The incidence of sepsis was 4.6%. Cardiac toxicity was the most common side effect of

anthracycline drugs. The R-CHOP regimen was the most commonly used regimen before transplantation, which contained doxorubicin. The patients typically received six cycles of chemotherapy pre-transplantation; therefore, the cumulative dose of anthracyclines was calculated to be within safe doses. All of the patients who received anthracycline drugs perform an ECG and echocardiography every three months. If the patients had heart disease (e.g., heart failure or a decreased left ventricular ejection fraction before induction therapy), anthracycline drugs were not administered to the patients, regardless of whether the patients were older than 60 years old. No one developed cardiac side effects after anthracycline-based induction chemotherapy. All patients assessed the cardiac function both before and after transplantation. Moreover, we also did not observe cardiac adverse events in these patients with HSCT during the long-term follow up periods. Our results showed that in addition of mitoxantrone did not increase cardiac issues compared to previous studies. Few patients exhibited liver or kidney toxicity following transplantation. No transplant-related mortality (TRM) was observed for all patients, indicating that the MCE conditioning regimen was well-tolerated.

Table 4
Adverse Events Associated with the MCE regimen

	N(%, n = 65)
Mucositisa (Grade III or IV)	5/65(7.7%)
Febrile neutropenia (Grade IV)	65/65(100%)
Sepsis	3/65(4.6%)
Nausea/vomiting	52/65(80%)
Cardiac toxicity	2/65(3.1%)
VOD	0/65(0)
CNS reactions	5/65(7.7%)

Survival analysis

We compared the survival data of these three groups (non-HSCT, upfront HSCT, and salvage HSCT). Of the 91 patients in the non-HSCT group, 14 patients died before the end point, 35 patients had undergone disease recurrence, the 1 year relapse rate was 15.4%, 2 year relapse rate was 24.2%, 3 year OS was 85%, 3 year PFS was 60.2%, 5 year OS was 75.5%, and 5 year PFS was 43.6%. In the upfront group, there were 55 patients, of which only 1 patient died before the end point, 5 patients underwent disease recurrence, the 1 year relapse rate was 1.8%, 2 year relapse rate was 7.3%, 3 year OS was 98%, 3 year PFS was 91.8%, 5 year OS was 98%, and 5 year PFS was 88.3%. There were only 10 patients in the salvage group, of which 5 patients died before the end point, 8 patients exhibited disease recurrence, the 1 year relapse rate was 30%, 2 year relapse rate was 70%, 3 year OS was 70%, 3 year PFS was 22.2%, 5 year OS was 46.2%, and 5 year PFS was 0%. All data were presented in Table 2, and there was a significant difference

between the upfront HSCT compared to non-HSCT and salvage HSCT group for several indicators (e.g., 1-year-relapse rate and 2-year-relapse rate, 3-year-OS, 3-year-PFS, 5-year-OS, and 5-year-PFS). The upfront HSCT group displayed a significant improvement in the OS (P = 0.001, median OS 117.8 m vs 78.1 m; Fig. 2) and PFS (P = 0.009, median PFS 92.9 m vs 48.9 m) compared to the non-HSCT group. the upfront HSCT group also showed significant improvement of OS (P = 0.000, median OS 117.8 m vs 58.3 m; Fig. 2) and PFS (P = 0.000, 92.9 m vs 21.5 m) compared to the salvage HSCT group.

Prognostic factors

The univariate and multivariate analysis of the upfront group revealed that the disease stage, IPI score, and BCL2 expression were prognostic factors related to the OS, age, disease stage, and C-myc expression were the prognostic factors relating to PFS. Patients with Ann Arbor Stage III (P = 0.00), lower IPI score (P = 0.03) and bcl2 (-) (P = 0.01) had a better prognosis for the OS of the upfront group. Patients with a younger age (P = 0.02) Ann Arbor Stage III (P = 0.00), and c-myc (-) (P = 0.03) had a better prognosis for PFS in the upfront group (Table 5).

Table 5
Multivariate Analysis of Patient Prognostic Factors

	OS			PFS	
	P value	HR(95%CI)		P value	HR(95%CI)
age	0.050	1.029(1.0-1.06)	age	0.018	0.960.92–0.99)
stage	0.000	0.424(0.30–0.60)	stage	0.000	0.09(0.03–0.24)
IPI score	0.029	0.496(0.26–0.93)	IPI score	0.535	0.79(0.37–1.67)
BCL2 expression	0.009	0.448(0.24–0.93)	BCL2 expression	0.167	0.56(0.25–1.28)
C myc expression	0.14	0.74(0.49–1.11)	C myc expression	0.029	0.38(0.16–0.91)
GCB	0.083	0.24(0.05–1.2)	GCB	0.98	0.76(0.35–1.69)
BM involvement	0.679	0.713(0.68–0.71)	BM involvement	0.488	0.98(0.35–1.64)

Discussion

HDC followed by ASCT may represent an effective means of reducing the tumor burden and residual tumors, which improved patient survival. In addition, HDC followed by ASCT resulted in an improved the prognosis compared to standard chemotherapy in patients with relapsed NHL [12, 21–24]. Several studies demonstrated that HDC followed by ASCT as consolidation therapy for patients who achieved CR following induction therapy could prolong the PFS, but not the OS [14, 25, 26]. In the treatment of T cell lymphoma and NK/T cell lymphoma, HDC followed by ASCT was recommended as a first line therapy after patients achieved a CR. In first line therapy for DLBCL, HDC followed by ASCT did not achieve a definitive result that this form of treatment could improve the prognosis of DLBCL after patients achieved

an initial CR. Anthracycline drugs (e.g., doxorubicin) were commonly used to treat DLBCL patients. In addition, some studies found that idarubicin was an important anthracycline drug in lymphoma chemotherapy. However, today, popular drug compositions consisting of a conditioning regimen do not typically include anthracycline drugs.

While anthracycline drugs were typically associated with the risk of causing cardiac toxicity following the accumulated dose of anthracyclines. Few reports demonstrated the efficacy and toxicity of the conditioning regimen, including anthracyclines. The conditioning regimen of BEAC is generally extremely effective and well-tolerated [15, 16, 27–30]. While the conditioning regimen (e.g., BEAC) provides a controversial result in the improvement of the DLBCL prognosis after the initial CR. If we modify the conditioning regimen, several problems existed. It was unknown whether the conditioning regimen, including anthracyclines, was safe and well-tolerated in ASCT, and if the conditioning regimen, including anthracyclines, could make a deeper response and improve the DLBCL prognosis in upfront HSCT. In this study, we found that the conditioning regimen consisting of mitoxantrone, cyclophosphamide, and etoposide was well-tolerated and hematological engraftment was similar to other conditioning regimen reports. As expected, the most frequently observed hematologic toxicity was febrile neutropenia (100%), which was higher than that of other reports [30–32], whereas other side effects was acceptable (e.g., nausea and vomiting) (grade 3–4, 80%), oral mucositis (grade 3–4, 7.7%), veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS, 0%), and central nervous system (CNS) adverse reactions (grade 1–2, 7.7%). There was no transplant-related mortality (TRM) for all patients. No patients exhibited significant liver or kidney toxicity, and most importantly, there was concern about the cardiac toxicity, the incidence of grade 1–2 was only 3.1%. In addition, after the long-term follow up, none of the patients developed cardiac dysfunction (e.g., clinically asymptomatic left ventricular systolic dysfunction [LVSD]), with a decrease in the left ventricular (LV) ejection fraction (EF) by > 10% points to a value of EF < 50% [33].

Another important finding was that the conditioning regimen of MCE followed by ASCT as an upfront treatment after patients first achieved CR and could significantly improve the PFS and OS, reduce the relapse rate in DLBCL patients compared with patients without HSCT. Upfront HSCT also improved the PFS and OS compared with salvage HSCT. In the upfront HSCT group, the 1 year relapse rate was 1.8%, 2 year relapse rate was 7.3%, 3 year OS was 98%, 3 year PFS was 91.8%, 5 year OS was 98%, 5 year PFS was 88.3%, the median OS was 117.8 m, and the median PFS was 92 m, which had superior outcome than previously reported other HSCT with the other conditioning regimen. Patients with Ann Arbor Stage III ($P = 0.00$), lower IPI score ($P = 0.03$), and bcl-2(-) ($P = 0.01$) had better prognosis for the OS in the upfront group. Patients who were younger ($P = 0.02$) Ann Arbor Stage III($P = 0.00$), and c-myc(-) ($P = 0.03$) had a better prognosis for PFS in the upfront group.

This study was limited by the small number of patients, particularly the number of patients in the salvage HSCT group. Moreover, whether upfront HSCT with the conditioning regimen MCE could substantially improve the DLBCL patients. This study only provides insight into the potential of the conditioning regimen of MCE in the treatment of DLBCL after the initial remission. This study also verified the

feasibility and safety of HDC followed by HSCT with conditioning regimen consisted of mitoxantrone, cyclophosphamide, and etoposide. Therefore, the conclusions should be verified in prospective, randomized, multicenter clinical trials, as further research should confirm the validity of this type of HSCT.

Conclusions

The upfront HSCT with MCE regimen achieved a complete hematopoietic engraftment and was well-tolerated. In addition, the conditioning regimen of MCE followed by ASCT as an upfront treatment after patients first achieved CR and could significantly improve the PFS and OS, reduce the relapse rate in DLBCL patients compared with patients without HSCT. Upfront HSCT also improved the PFS and OS compared with salvage HSCT. However, whether high-risk DLBCL should receive consolidation HSCT with an MCE regimen after an initial CR requires a prospective, large-scale, long-term clinical trials to validate.

List Of Abbreviations

ASCT	autologous hematopoietic stem cell transplantation
HSCT	hematopoietic stem cell transplantation
DLBCL	diffuse large B cell lymphoma
MCE	mitoxantrone, etoposide, and cyclophosphamide
OS	overall survival
PFS	progression-free survival
CR	complete remission
PR	partial remission
SD	stable disease
PD	progressive disease
ORR	objective response rate
IPI	international prognostic index
HDC	High-dose chemotherapy
NHL	non-Hodgkin lymphoma
SOC	standard of care
RCTs	randomized clinical trials
BuCyE	busulfan, cyclophosphamide, and etoposide
Benda-EAM	bendamustine, etoposide, cytarabine, and melphalan
IIVP	ifosfamide, idarubicin, and etoposide
R/R NHL	recurrent or refractory non-Hodgkin lymphoma
PLT	Platelet
NCCN	National Comprehensive Cancer Network
PET/CT	positron emission tomography computed tomography
TRM	transplant-related mortality
VOD/SOS	veno-occlusive disease/sinusoidal obstruction syndrome
CNS	central nervous system
LVEF	Left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction

Declarations

Ethics approval and consent to participate

The study protocols were approved by the Ethical Committee of Huadong Hospital with the Ethical number of 2021K126. The patients provided written infomed consent. This clinical investigation was conducted according to the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

Jiexian Ma and Yanhui Xie contributed to the conception and design; Jiexian Ma, Huying Wei, Pingping Chen, Mingyue Chen, Lin Shen, Min Wu, Wensi Qian and Wulipan fulati contributed to the acquisition of data; Jiexian Ma, Huying Wei and Shunrong Sun contributed to the analysis and interpretation of data; Jiexian Ma, Yanhui Xie and Shunrong Sun contributed to the writing, review, and/or revision of the manuscript; Zilan Huang contributed to the administrative, technical, or material support; Yanhui Xie and Jiexian Ma supervised the study. Jiexian Ma and Shunrong Sun have contributed equally to this work. The authors read and approved the final manuscript.

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Figures

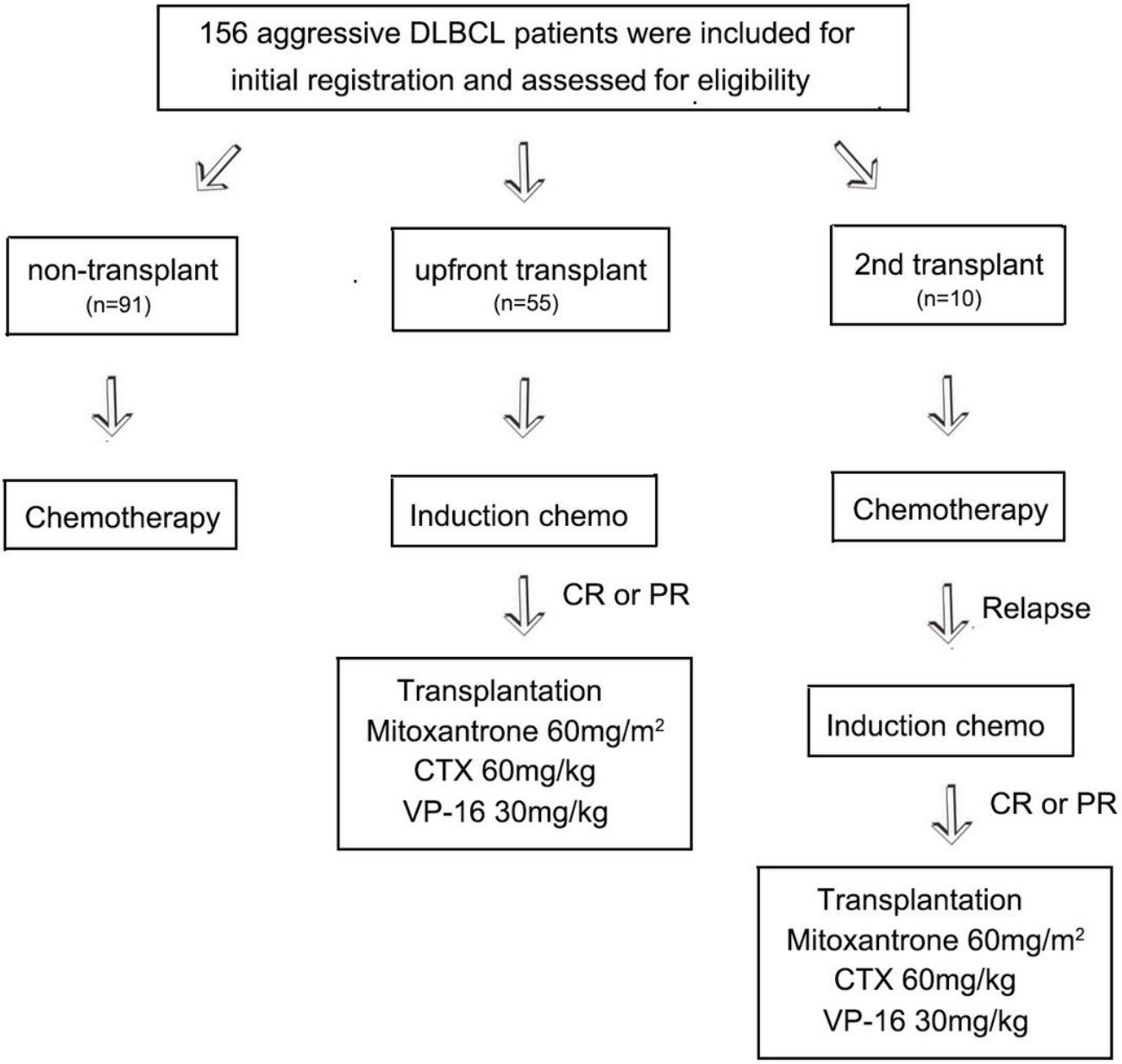

Figure 1

The flow diagram of the treatment used this study

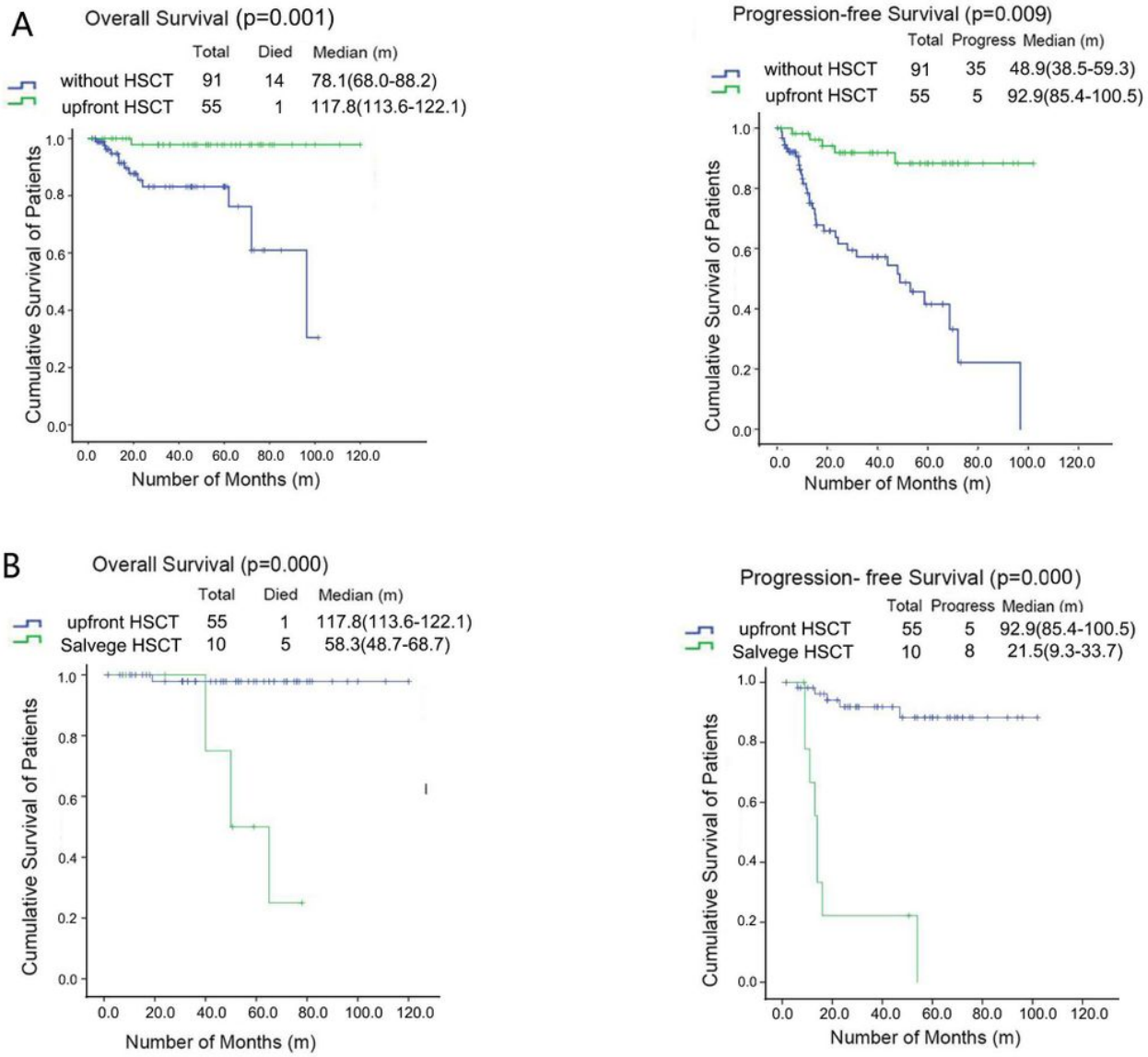

Figure 2

Comparison of OS and PFS between the different groups: A. Comparison of the OS and PFS between the non-HSCT group and upfront HSCT group. B. Comparison of the OS and PFS between the upfront HSCT group and salvage HSCT group.