



Nitrosourea, etoposide and cyclophosphamide followed by autologous stem cell transplantation for pediatric lymphoma patients

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Abstract

Treatment outcomes in pediatric lymphoma have improved substantially over the past 2 decades; however, the prognosis for patients with high risk or relapsed disease remains poor. We evaluated outcomes of high-dose chemotherapy (HDC) and autologous stem cell transplantation (auto-SCT) in 56 pediatric lymphoma patients. Patients received nitrosourea (51 BCNU; 5 ACNU), etoposide, and cyclophosphamide (BEC; AEC). Median age at HDC/auto-SCT was 12 years (range 2–17 years). Forty-four patients underwent HDC/auto-SCT because they did not achieve complete remission after induction chemotherapy. Eight patients showed relapse and four NK/T-cell lymphoma patients also underwent HDC/auto-SCT. BCNU pneumonitis was diagnosed in nine (16.0%) patients. Eight (14.3%) relapsed after HDC/auto-SCT. Treatment-related mortality occurred in three cases. Five-year event-free survival and overall survival rates were 74.8% [72.7% non-Hodgkin's lymphoma (NHL); 83.3% Hodgkin's disease (HD); 72.7%] and 83.6% (81.6% NHL; 91.7% HD), respectively. HDC/auto-SCT with BEC or AEC regimen for pediatric high-risk lymphoma patients showed feasible outcomes. However, treatment modifications are warranted to reduce relapse and toxicity.

Keywords Lymphoma · Carmustine · Pediatric · Autologous stem cell transplantation

Introduction

Lymphomas (Hodgkin and non-Hodgkin) are the third most common malignancy after leukemia and brain tumor in pediatric patients. Non-Hodgkin's lymphoma (NHL) accounts for approximately 60% of malignant lymphomas and Hodgkin's disease (HD) accounts for the rest. The 2008 WHO classification defines the following major histological subtypes of NHL: precursor lymphoid neoplasm with subtypes including B-cell and T-cell lymphoblastic lymphoma (B-LBL and T-LBL); mature B-cell neoplasm with subtypes including Burkitt lymphoma (BL); diffuse large B-cell lymphoma (DLBCL); and mature T-cell and NK/T-cell neoplasms with

subtypes including anaplastic large cell lymphoma (ALCL) and extranodal NK/T-cell lymphoma (NKTL) [1]. Compared with adult lymphomas, pediatric NHL more often presents as high-grade tumors with disseminated disease and distant metastasis [2].

The prognosis of newly diagnosed pediatric NHL and HD has improved significantly. Event-free survival (EFS) rate for NHL has increased to 60–95% during the past 2 decades [3–6]. Recent studies have shown long-term EFS rates of over 80% in pediatric patients with HD [7]. These results have been achieved through collaboration study and risk stratification strategy [8, 9]. Previous studies have reported that an early response to chemotherapy is one of the prognostic markers of B-cell NHL and acute lymphoblastic leukemia [10]. However, the prognosis for children with relapsed or refractory HD and NHL is poor with the current intensive regimens [11]. NKTL is a rare subtype of pediatric NHL and is known to have a highly aggressive clinical course. However, as data for pediatric NKTL are limited, no optimal treatment is available [12, 13]. High-dose chemotherapy (HDC) and autologous stem cell transplantation (auto-SCT) have been used to improve outcomes

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for lymphoma patients with poor prognosis. Therefore, we used HDC/auto-SCT in pediatric lymphoma patients who achieved partial response (PR) after induction chemotherapy, NKTL patients, and patients showing recurrence after conventional chemotherapy.

1,3-Bis (2-chloroethyl)-1-nitrosourea (BCNU), etoposide, and cyclophosphamide (BEC) is one of the commonly used conditioning regimens in relapsed or refractory lymphoma in pediatric patients [14, 15]. At our institution, we used BEC or 1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU), etoposide, and cyclophosphamide (AEC) conditioning regimens in high-risk lymphoma patients. Therefore, we performed a retrospective review of all children and adolescents with lymphoma receiving HDC/auto-SCT at Seoul National University Children's Hospital.

Patients and methods

Patients and study design

This retrospective study included 56 pediatric lymphoma patients who received HDC and underwent auto-SCT at Seoul National University Children's Hospital between December 2001 and February 2016. In our center, HDC/auto-SCT was used for patients showing PR after induction chemotherapy, patients who showed relapse after showing complete response (CR), and patients diagnosed with NKTL which is known to have an aggressive clinical course. Disease stage at diagnosis was determined by the Ann Arbor staging system for HD and St. Jude staging system for NHL [16]. Response evaluation was done using bone scan and computed tomography or magnetic resonance imaging. Positron emission tomography was used since November 2009. A CR was defined as the total disappearance of all tumors and no evidence of disease; a PR was defined as a $\geq 50\%$ decrease in tumor size and no new lesions; and progressive disease was defined as a $\geq 25\%$ increase in tumor size or the appearance of a new lesion. A CR1 was defined as the CR achieved in a patient receiving first-line chemotherapy. A CR2 or CR3 was defined as the CR achieved in a patient receiving second- or third-line chemotherapy, who had shown relapse or disease progression. Patient characteristics are listed in Table 1.

Peripheral blood stem cell (PBSC) mobilization

All patients received cyclophosphamide 1000 mg/m²/day and etoposide 150 mg/m²/day on days 0, 1, and 2 for PBSC mobilization. Granulocyte colony-stimulating factor

Table 1 Characteristics of the 56 patients receiving HDC and auto-SCT

Characteristics	Data
Age (years), median (range), at diagnosis	11.5 (1.9–16.9)
Age (years), median (range), at transplantation	12.7 (2.5–17.6)
Gender, no. (%)	
Male	32 (57.1)
Female	24 (42.9)
Stage, no. (%), at diagnosis	
I	2 (3.6)
II	6 (10.7)
III	21 (37.5)
IV	27 (48.2)
Histologic subtype, no. (%)	
Hodgkin's disease	12 (21.4)
Burkitt lymphoma	12 (21.4)
Anaplastic large cell lymphoma	10 (17.9)
Lymphoblastic lymphoma	9 (16.1)
Diffuse large B-cell lymphoma	8 (14.3)
NK/T-cell lymphoma	4 (7.1)
Subcutaneous panniculitis T-cell lymphoma	1 (1.8)
Involvement, no. (%), at diagnosis	
BM	16 (28.6)
CNS	4 (7.1)
Indication for auto-SCT, no. (%)	
Not achieving a CR after induction chemotherapy	44 (78.6)
Relapse	8 (14.3)
NK/T-cell lymphoma	3 (5.4)
NK/T-cell lymphoma + Relapse	1 (1.8)
Adjuvant radiation therapy (RT), no. (%)	
Local RT	9 (16.1)
Craniospinal RT	2 (3.6)
Cranial RT	1 (1.8)

(G-CSF, 10 µg/kg) was administered from day 7 until the end of PBSC mobilization. The target CD34+ cell count was 4×10^6 /kg. Patients who did not collect enough cells received plerixafor, a C-X-C motif chemokine receptor 4 antagonist, and G-CSF for PBSC mobilization.

Transplant conditioning regimen

All patients received cyclophosphamide 1500 mg/m²/day on days - 5, - 4, - 3, and - 2 and etoposide 800 mg/m²/day on days - 8, - 7, and - 6. Fifty-one and five patients received BCNU and ACNU 150 mg/m²/day, respectively, on days - 8, - 7, and - 6. All patients received methylprednisolone to protect against pulmonary toxicity as follows: 1 mg/kg/day on days - 9 to - 2, then tapered off over 6 days.

G-CSF support

Patients received 300 $\mu\text{g}/\text{m}^2$ G-CSF daily, since the day when absolute neutrophil count (ANC) was found to be less than $500/\text{mm}^3$ after stem cell infusion. G-CSF was administered until the ANC reached more than $3.0 \times 10^9/\text{l}$ for 1 day or $1.0 \times 10^9/\text{l}$ for 3 consecutive days.

Engraftment

The first 3 consecutive days with an ANC of more than $0.5 \times 10^9/\text{l}$ and $1.0 \times 10^9/\text{l}$ and the first 3 consecutive days with a platelet count of more than $20 \times 10^9/\text{l}$ and $50 \times 10^9/\text{l}$ without platelet transfusion for at least 7 days were defined as the times for neutrophil and platelet engraftment, respectively.

Complications

Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03, Washington, DC, USA). Hepatic veno-occlusive disease (VOD) was diagnosed clinically in patients satisfying two or more criteria based on the Baltimore criteria or modified Seattle criteria [17, 18]. Pulmonary VOD was diagnosed clinically in patients who had pulmonary hypertension and showed radiological findings of pulmonary edema with no evidence of left-ventricular dysfunction [19, 20]. Pneumonitis due to BCNU was clinically defined as the condition when patients had respiratory symptoms (dyspnea and cough) and showed bilateral diffuse infiltrates on computed tomography without an infectious etiology.

Statistical analysis

Statistical analyses were performed using R version 3.5.0 (Bell Laboratories, New Jersey, USA). Overall survival (OS) was calculated from the date of auto-SCT to death or the last follow-up. EFS was calculated from the date of auto-SCT to the date of event or the last follow-up if the patient did not experience any events. Events were defined as relapse, secondary malignancy, relapse of primary malignancy, treatment-related mortality (TRM), or death due to any cause. Logistic regression was used to analyze risk factors for drug-induced pneumonitis. The Kaplan–Meier method and log-rank test were used to estimate and compare probabilities of survival. TRM and relapse were calculated using the cumulative incidence function [21]. The Fine and Gray regression model was used to evaluate the predictive factors for relapse [22].

Ethics statement

All patients and their parents provided informed consent for the treatments and procedures of HDC/auto-SCT. This retrospective study was approved by the institutional review board (IRB number: 1608-070-784).

Results

Baseline characteristics

During the study period, the histological subtypes of lymphoma in the patients who received HDC and underwent auto-SCT were as follows: LBL 9 (B-LBL 4; T-LBL 5); BL 12; DLBCL 8; ALCL 10; NKTL 4; other NHLs (subcutaneous panniculitis T-cell lymphoma) 1; and HD 12. Of the eight DLBCL patients, five primary mediastinal large B-cell lymphoma (PMBCL) patients were included. One of the eight DLBCL patients was diagnosed with Epstein–Barr virus-associated DLBCL during maintenance chemotherapy of acute lymphoblastic leukemia. Median age at diagnosis and HDC/auto-SCT was 11.5 (range 1.9–16.9) and 12.7 (range 2.5–17.6) years, respectively. Median time from diagnosis to transplantation was 9.4 months (range 5.7–71.0 months). Patients received conventional chemotherapy from previous prospective studies according to risk group and histological type before undergoing HDC/auto-SCT [7, 10, 23–25]. For nine of 56 patients who relapsed after first CR, median time from diagnosis to relapse was 12.2 months (range 4.0–54.0 months). Two of 56 patients failed to collect sufficient PBSCs using chemotherapy and G-CSF. They succeeded in harvesting PBSCs using plerixafor and G-CSF. Forty-eight patients achieved a CR prior to SCT and the remaining eight patients had a PR. All patients received the same conditioning regimen containing nitrosourea, cyclophosphamide, and etoposide. Patient characteristics are demonstrated in Table 1.

Engraftment

Median number of infused CD34+ cells was $10.15 \times 10^6/\text{kg}$ (range 0.39 – $101.66 \times 10^6/\text{kg}$). All patients underwent engraftment for both neutrophils and platelets except for one who died before engraftment. Median number of days to achieve an ANC more than $0.5 \times 10^9/\text{l}$ and $1.0 \times 10^9/\text{l}$ for 3 consecutive days was 11 days (range 9–15 days) and 11 days (range 9–16 days), respectively. Median number of days to achieve a platelet count more than $20 \times 10^9/\text{l}$ and $50 \times 10^9/\text{l}$ was 15 days (range 12–45 days) and 18 days (range 13–49 days), respectively.

Toxicity and TRMs

Drug-induced pneumonitis was diagnosed in nine patients, of which one died of respiratory failure. The patient who experienced respiratory failure did not undergo bronchoalveolar lavage due to high ventilator setting. Median time to the development of pneumonitis was 36 days (range 26–55 days) (Table 2). Sex, age, prior bleomycin exposure, prior chest or craniospinal irradiation, and prior rituximab exposure were the variables used to analyze risk factors for drug-induced pneumonitis; however, no significant risk factor was found. Two of five patients receiving ACNU developed pulmonary VOD. None of the patients receiving BCNU developed pulmonary VOD, but two developed hepatic VOD. Fifty-three patients developed febrile neutropenia. Bacteremia occurred in ten patients before engraftment. Cytomegalovirus infection developed in 24 patients, of which 1 was suspected to develop cytomegalovirus pneumonitis. Grade 3 alanine aminotransferase and aspartate aminotransferase elevation occurred in two patients. No patients had grade 3 or higher blood bilirubin and creatinine elevation. Grade 5 acute respiratory distress syndrome occurred in one patient. Two patients developed secondary malignancy: one patient developed acute myeloid leukemia 7 months after HDC/auto-SCT and one patient developed colon adenocarcinoma 9 years after HDC/auto-SCT. One patient was diagnosed with interstitial lung disease 4 years after HDC/auto-SCT and underwent lung transplantation 11 years after HDC/auto-SCT. Three patients died of treatment-related complications: respiratory failure one; pulmonary VOD one; and secondary acute myeloid leukemia one. The cumulative incidence of TRM was 5.4%.

Relapse, progression, and risk factors for relapse

Eight patients (T-LBL 1, BL 1, DLBCL 2, ALCL 1, NKTL 1, and HD 2) experienced relapse at a median time of 9.8 months (range 1.1–44.4 months) after HDC/auto-SCT. The cumulative incidence of relapse was 13.8%. Five of eight patients had CR whereas the rest had PR at the time of HDC/auto-SCT. In univariate analysis, no significant risk factors for relapse were found. In multivariate analysis, which included factors with $p < 0.4$ in the univariate analysis, pre-SCT status was the only significant risk factor for relapse (Table 3). Four of eight patients died of disease progression. Two patients were lost to follow-up. The remaining two patients were alive with no evidence of disease after receiving chemotherapy and allogeneic SCT (1 unrelated and 1 haploidentical).

Event-free survival and overall survival

Events occurred in 14 patients: relapse 8; TRM 3; secondary malignancy 2 (acute myeloid leukemia 1; colon adenocarcinoma 1); and relapse of primary malignancy 1. Overall, 48 (NHL 37; HD 11) of 56 patients who received HDC/auto-SCT survived. Median follow-up duration was 42.9 months (range 0.2–180.8 months). The 5-year EFS and OS rates in all patients were 74.8% and 83.6%, respectively (Fig. 1). The 5-year EFS and OS rates by histological subtypes were 72.7% and 81.6% for NHL (76.2% and 74.1% for LBL, 72.7% and 90.0% for BL/DLBCL, 83.3% and 91.7% for ALCL) and 83.3% and 91.7% for HD, respectively (EFS $p = 0.560$; OS $p = 0.504$) (Fig. 1). The 5-year EFS and OS rates for different indications were as follows: PR after induction chemotherapy 74.1% and 86.1%; relapse 83.3% and 83.3%; and NKTL 75.0% and 75.0%, respectively (EFS $p = 0.499$; OS $p = 0.721$). The 5-year EFS and OS rates for pre-SCT status were as follows: CR1, 76.2% and 87.3%; CR2-3, 83.3% and 83.3%; and PR, 62.5% and 75.0%, respectively (EFS $p = 0.448$; OS $p = 0.851$).

Outcome by histological subgroup

We classified all patients according to the histological subtypes of lymphoma, reason for undergoing HDC/auto-SCT, and pre-auto-SCT disease status. Table 4 shows outcomes of each group.

Discussion

This retrospective study reviewed the single-center data of 56 lymphoma patients who were expected to have poor outcomes and received AEC or BEC conditioning chemotherapy followed by HDC/auto-SCT. Most patients (85.7%) included had advanced stage (stage III or IV) disease. Response to chemotherapy is one of the most important prognostic factors; minimal disseminated disease after chemotherapy may have a prognostic role in pediatric lymphoma [26–28]. Here, we aimed to improve treatment outcomes in patients having residual disease after receiving induction chemotherapy, patients with NTKL, and patients with recurrent disease using HDC/auto-SCT. Consequently, patients showing different indications for HDC/auto-SCT showed 5-year EFS values of 50.0–83.3% and 5-year OS values of 75.0–86.1%. In the previous studies, the 3- or 5-year EFS rate was reported to be 53–66% in relapsed/refractory pediatric lymphoma patients who received HDC/auto-SCT [15, 29]. Our study showed a promising outcome of 83.3% EFS rate in relapsed pediatric lymphoma patients, although there is a limitation of small number of patients.

Table 2 Clinical features of patients suspected with BCNU-induced pneumonitis

Patient sex/age	Disease subtype	Days from HDC/auto-SCT	# of events	Symptoms	Radiologic findings	Prior chest RT	Prior bleomycin	Prior rituximab	Corticosteroid therapy	Outcome
F/13.1	BL	37	1	Fever, cough	Bilateral multifocal patchy GGO, pleural effusion	(-)	(-)	(-)	(-)	Recovered
F/17.3	DLBL	55	1	Fever, blood-tinged sputum	Multifocal patchy GGO, pleural effusion	(-)	(-)	(-)	(-)	Recovered
M/6.2	HD	26	1	Fever	Bilateral interlobular septal thickening, pleural effusion	(-)	(+)	(-)	(-)	ILD
M/3.6	ALCL	26	1	Fever, tachypnea	Bilateral multifocal nodular consolidations and GGO	(-)	(-)	(-)	(-)	Dead
M/14.1	HD	44	1	Fever, cough, dyspnea	Bilateral patchy GGO, pleural effusion	(-)	(+)	(-)	(-)	Recovered
M/17.1	DLBL	48	1	Fever, chest pain, dyspnea	Bilateral patchy GGO, pleural effusion	(-)	(-)	(-)	(-)	Recovered
M/4.0	BL	30	1	Fever, cough, sputum	Bilateral patchy GGO	(-)	(-)	(-)	(-)	Recovered
M/13.3	HD	34	2	Dyspnea	Bilateral multifocal patchy GGO, pleural effusion	(-)	(+)	(-)	(+)	Recovered
M/13.5	DLBL	38	1	Sputum	Bilateral multifocal GGO	(-)	(-)	(+)	(+)	Recovered

ALCL anaplastic large cell lymphoma, BAL bronchoalveolar lavage, BL Burkitt lymphoma, DLBL diffuse large B-cell lymphoma, GGO ground glass opacity, HD Hodgkin's disease, ILD interstitial lung disease

Table 3 Univariate and multivariate analyses of predictive factors for relapse

	No. (%)	Univariate		Multivariate	
		<i>p</i>	Relative risk (Exp[<i>b</i>])	<i>p</i>	Relative risk (Exp[<i>b</i>])
Sex					
M	32 (57.1)				
F	24 (42.9)	0.26	0.41	0.18	0.34
Age at HDC/auto-SCT					
< 10	23 (41.1)				
≥ 10	33 (58.9)	0.29	2.31	0.31	2.39
Histology					
Hodgkin's disease	12 (21.4)				
Non-Hodgkin's lymphoma	44 (78.6)	0.73	0.76		
Stage					
I–III	29 (51.8)				
IV	27 (48.2)	0.54	0.63		
Indication for HDC/auto-SCT					
PR after induction CTx	44 (78.6)				
Relapse	8 (14.3)	0.81	0.79		
NK/T-cell lymphoma	4 (7.1)	0.48	2.16		
Pre-HDC/auto-SCT disease status					
CR	48 (85.7)				
PR	8 (14.3)	0.068	3.96	0.045	4.85

CR complete response, CTx chemotherapy, HDC/auto-SCT high-dose chemotherapy and autologous stem cell transplantation, PR partial response

However, recurrence was a major cause of treatment failure and patients who showed relapse after HDC/auto-SCT had dismal outcomes. Eight of 56 patients showed relapse after HDC/auto-SCT and only two patients were alive without any evidence of disease. We performed univariate and multivariate analyses to determine predictive factors for relapse. In multivariate analyses, patients having PR before HDC/auto-SCT had a higher risk of relapse (relative risk 4.85; 95% confidence interval 1.03–22.78) than patients having CR before HDC/auto-SCT. Sex, age, histological type (HD or NHL), and indication for HDC/auto-SCT were not associated with recurrence, but further analysis is needed in a large patient group.

One of the five T-LBL patients showed recurrence and this patient had undergone HDC/auto-SCT because of relapse after conventional chemotherapy. The patient eventually died of disease progression and infection. Currently, it is considered that allogeneic SCT results in a superior outcome than HDC/auto-SCT in LBL, with patients achieving second CR [30]. Contrastingly, all three patients with stage III T-LBL who underwent HDC/auto-SCT showed long-term survival, therefore HDC/auto-SCT may be a treatment option in patients who showed response to chemotherapy and had no bone marrow or central nervous system involvement.

Only 1 of 12 BL patients showed recurrence at 1 month after HDC/auto-SCT and this patient had PR before HDC/auto-SCT. He showed rapid disease progression and poor prognosis. HDC/auto-SCT is recommended for BL patients achieving second CR and researchers have reported that there was no difference between the outcome of allogeneic and autologous SCT [31]. Addition of rituximab to the treatment regimen has also improved survival rates in group C BL patients who have central nervous system disease and/or bone marrow involvement [32]. Incorporation of rituximab in conventional chemotherapy before HDC/auto-SCT may benefit high-risk BL patients (by reducing the proportion of patients undergoing HDC/auto-SCT by increasing the remission rate or improving the outcome of HDC/auto-SCT).

PMBCL patients had worse outcomes compared to other DLBCL patients [33, 34]. Recently, the efficacy of rituximab in pediatric PMBCL patients has been reported [35, 36]. We included five PMBCL patients, of which two showed recurrence. Patients showing recurrence did not receive rituximab with conventional chemotherapy before HDC/auto-SCT unlike the patients who did not show recurrence. Therefore, HDC/auto-SCT after rituximab-associated chemotherapy may improve the outcome of pediatric DLBCL patients.

Previous studies have described variable outcomes in ALCL patients. Fanin et al. emphasized that HDC/auto-SCT

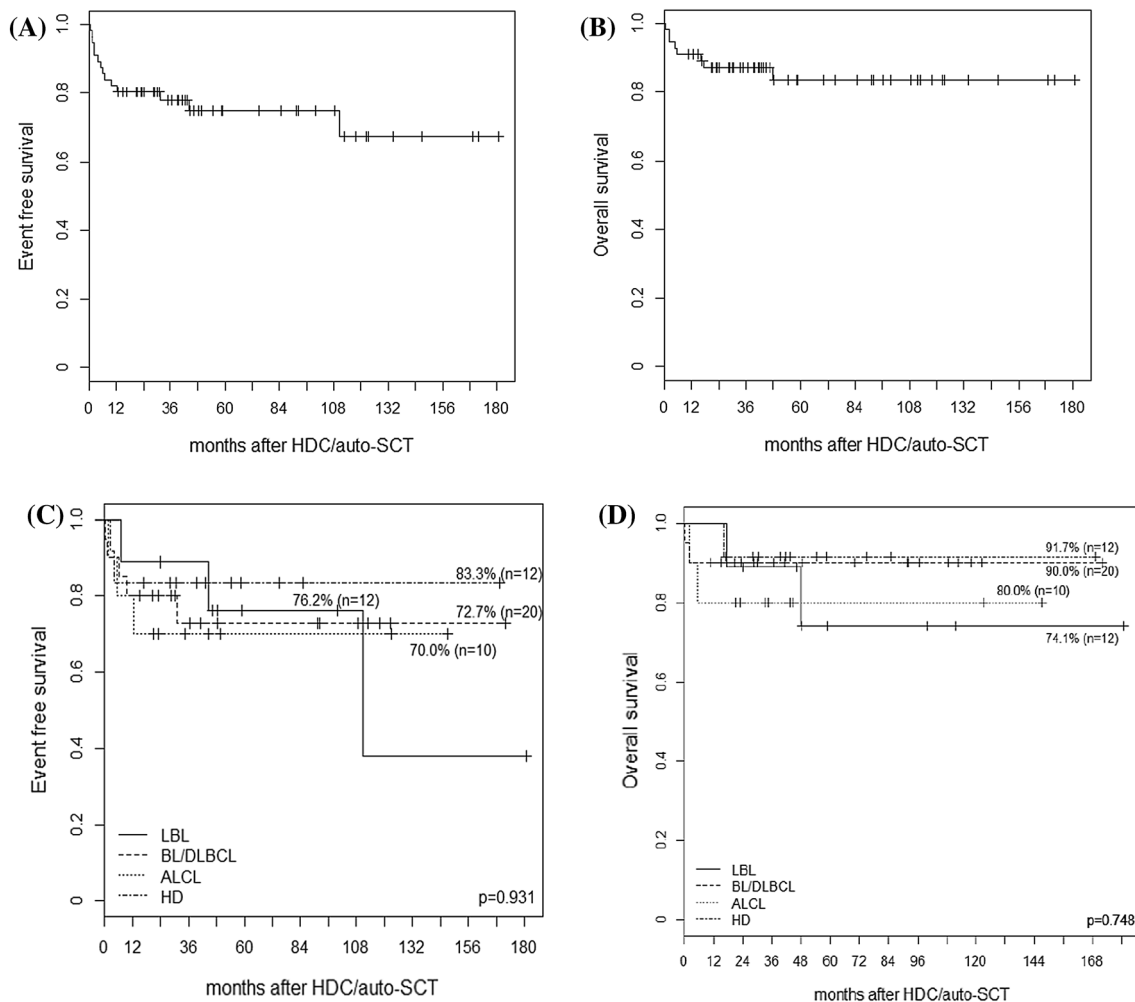


Fig. 1 Survival of pediatric lymphoma patients who underwent high-dose chemotherapy and autologous stem cell transplantation. **a** Five-year event-free survival (EFS) was 74.8%. **b** Five-year overall survival (OS) was 83.6%. **c** Five-year EFS for lymphoblastic lymphoma (LBL), Burkitt lymphoma/diffuse large B-cell lymphoma (BL/

DLBCL), anaplastic large cell lymphoma (ALCL) and Hodgkin's disease (HD) was 76.2%, 72.7%, 70.0% and 83.3%, respectively. **d** Five-year OS for LBL, BL/DLBCL, ALCL and HD was 74.1%, 90.0%, 80.0% and 91.7%, respectively

consolidated the response to chemotherapy in patients who were transplanted in CR or PR, but did not change the response in refractory/resistant or relapsed cases [37]. In our study, HDC/auto-SCT was performed in two ALCL patients who had PR before transplantation, one of whom showed relapse and died while the other lived with no evidence of disease. Recently, anti-CD30 monoclonal antibodies such as brentuximab and anaplastic lymphoma kinase inhibitors such as crizotinib have shown promising results in refractory ALCL [38, 39]. Therefore, further studies are needed to determine the effectiveness of autologous or allogeneic SCT and new drug combinations in patients with a high risk of relapse.

Among HD patients, two patients with stage IV disease showed recurrence, of which one patient recovered after haploidentical PBSCT; however, the other patient died

of disease progression although he underwent unrelated PBSCT. Several studies have reported the benefits of allogeneic SCT in patients showing recurrence after HDC/auto-SCT [40]. After a phase 3 study, brentuximab was approved for maintenance therapy after HDC/auto-SCT in patients with a high risk of relapse or progression [41]. Pembrolizumab showed a response rate of 69% in relapsed or refractory HD patients, most of whom had undergone HDC/auto-SCT and then received brentuximab therapy [42]. However, studies including pediatric patients and involving this new treatment paradigm are still lacking and data on long-term follow-up and comparison between allogeneic and autologous SCT are needed.

Nitrosourea can cause severe pulmonary toxicity [43]. The total BCNU dose of 450 mg/m² in BEC conditioning regimen was known to be the upper limit dose to minimize

Table 4 Subgroups based on stage of disease, indication for HDC/auto-SCT and disease status at transplantation

Diagnosis	Stage	Reason for auto-SCT	Pre-SCT status	No. (%)	Transplantation outcome (no.)	Current status (no.)	5-year EFS/OS (%)
B-LBL	IV	PR	PR	1 (1.8)	CR (1)	NED (1)	
	IV	PR	CR1	3 (5.4)	CR (3)	NED (3)	
T-LBL	III	PR	CR1	3 (5.4)	CR (2), secondary AML (1)	NED (2) Dead (1)	
	III	PR	PR	1 (1.8)	CR (1)	NED (1)	
	III	relapse	CR2	1 (1.8)	Relapse (1)	Dead (1)	
				9 (16.1)	CR (7), relapse(1), secondary AML (1)	NED (7), Dead (2)	76.2/74.1
BL	III	PR	CR1	3 (5.4)	CR (3)	NED (3)	
	III	relapse	CR2	1 (1.8)	CR (1)	NED (1)	
	IV	PR	CR1	4 (7.1)	CR (3), TRM (1)	NED (3), Dead (1)	
	IV	PR	PR	3 (5.4)	CR (2), relapse (1)	NED (2), Dead (1)	
	IV	relapse	CR2	1 (1.8)	CR (1)	NED (1)	
				12 (21.4)	CR (10), relapse (1), TRM (1)	NED (10), Dead (2)	83.3/83.3
DLBL	II	PR	CR1	2 (3.6)	CR (2)	NED (2)	
	III	PR	CR1	5 ^a (8.9)	Relapse (2) ^b , CR (3)	NED (4), F/U loss (1)	
	IV	PR	CR1	1 (1.8)	Relapse of primary disease (1)	NED (1)	
				8 (14.3)	CR (5), relapse (2), primary disease relapse (1)	NED (7), F/U loss (1)	50.0/100.0
ALCL	III	PR	CR1	3 (5.4)	CR (3)	NED (3)	
	III	PR	PR	1 (1.8)	Relapse (1)	F/U loss (1)	
	III	Relapse	CR3	1 (1.8)	CR (1)	NED (1)	
	III	Relapse	PR	1 (1.8)	CR (1)	NED (1)	
	IV	PR	CR1	4 (7.1)	CR (2), TRM (2)	NED (2), Dead (2)	
				10 (17.9)	CR (7), TRM (2), relapse(1)	NED (7), Dead (2), F/U loss (1)	70.0/80.0
NKTL	I	NKTL, Relapse	CR2	1 (1.8)	CR (1)	NED (1)	
	I	NKTL	CR1	1 (1.8)	CR (1)	NED (1)	
	II	NKTL	CR1	1 (1.8)	Relapse (1)	Dead (1)	
	III	NKTL	CR1	1 (1.8)	CR (1)	NED (1)	
				4 (7.1)	CR (3), relapse (1)	NED (3), Dead (1)	75.0/75.0
HD	II	PR	CR1	1 (1.8)	CR (1)	NED (1)	
	II	Relapse	CR2	2 (3.6)	CR (2)	NED (2)	
	IV	PR	CR1	8 (14.3)	CR (7), relapse (1) ^c	NED (8)	
	IV	PR	PR	1 (1.8)	Relapse (1) ^d	Dead (1)	
				12 (21.4)	CR (10), relapse (2)	NED (11), Dead (1)	83.3/91.6

One patient with subcutaneous panniculitis T-cell lymphoma was not included in the table

ALCL anaplastic large cell lymphoma, AML acute myeloid leukemia, auto-SCT autologous stem cell transplantation, BL Burkitt lymphoma, DLBL diffuse large B-cell lymphoma, HD Hodgkin's lymphoma, HDC High-dose chemotherapy, LBL lymphoblastic lymphoma, NED no evidence of disease, NKTL NK/T-cell lymphoma, TRM treatment-related mortality

^aPrimary site of disease was the mediastinum for all 5 stage III DLBCL patients

^bOne of the two patients who relapsed after HDC/auto-SCT had no evidence of disease after chemotherapy and haploidentical peripheral blood stem cell transplantation (hPBSCT). The other patient was lost to follow-up

^cThe patient underwent hPBSCT

^dThe patient underwent unrelated PBSCT

pulmonary toxicity, thus we used a total dose of 450 mg/m² ACNU or BCNU [44, 45]. However, patients who received this total dose developed pulmonary toxicity; the crude incidence of drug-induced pneumonitis was 16% in our center. Richard et al. reported that the BCNU dose of 300 mg/m² in BEC conditioning regimen was well tolerated and was not associated with any reduction in efficacy [15]. Lane et al. reported that pneumonitis is a significant cause of death in patients who received BCNU, and furthermore prior mediastinal radiation therapy is a risk factor of pneumonitis [46]. In our study, we did not find a relationship between pneumonitis and prior exposure to bleomycin or rituximab, or chest or craniospinal irradiation before HDC/auto-SCT because the number of patients in each group was small. The pathogenesis of BCNU pneumonitis has not yet been elucidated. As seen in this study, it is difficult to predict the development of BCNU pneumonitis based on the BCNU dose, prior mediastinal radiation therapy, and so on. BCNU pneumonitis tends to be self-limiting in most patients, but it is important to note that it may result in mortality in rare cases. Although it has been known that BCNU can cause pulmonary toxicity, there have been no previous reports of ACNU increasing the risk of pulmonary VOD as far as we know. However, more attention should be paid to pulmonary VOD when administering high-dose ACNU.

This study has limitations. This is a retrospective study and patients who received HDC and underwent auto-SCT were analyzed. It covers various subtypes of lymphomas, so it is difficult to assess the role of HDC/auto-SCT in treating NKTL patients, who were few. However, the study's strength is that all patients were administered the same conditioning regimen for long-term periods.

In conclusion, HDC/auto-SCT with BEC or AEC conditioning regimen is a feasible treatment option for pediatric lymphoma patients. However, efforts to reduce TRM, strategies to reduce recurrence after HDC/auto-SCT, and close monitoring of long-term complications such as secondary malignancies are needed. Furthermore, novel treatment strategies are required to overcome poor outcomes in patients who show relapse after auto-SCT. Further studies and new strategies such as allogeneic SCT, upfront target therapy, and immunotherapy are needed to improve survival rates in high-risk lymphoma patients.

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Compliance with ethical standards

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

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