ORIGINAL ARTICLE

Treatment with intravenous busulfan, melphalan, and etoposide followed by autologous stem cell transplantation in patients with non-Hodgkin's lymphoma: a multicenter study from the consortium for improving survival of lymphoma

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SUMMARY

Several high-dose therapy (HDT) conditioning regimens have been used to treat non-Hodgkin's lymphoma (NHL), such as bis-chloroethylnitrosourea (BCNU)/etoposide/cytosine arabinoside/melphalan (BEAM), BCNU/etoposide/cytosine arabinoside/cyclophosphamide (BEAC), and cyclophosphamide/BCNU/etoposide (CBV). BCNU is an active drug in HDT of NHL, but the supply is limited in some countries, including Korea. Busulfan has been used in allogeneic and autologous stem cell transplantation (ASCT). This phase II study evaluated the efficacy of busulfan/melphalan/etoposide (BuME) as a conditioning regimen for HDT in relapsed or high-risk NHL. The regimen consisted of intravenous busulfan (3.2 mg/kg/day) on days −8, −7, and −6, etoposide (400 mg/m^2/day) on days −5 and −4, and melphalan (50 mg/m^2/day) on days −3 and −2. A total of 46 patients were included in the study, with 36 (78.3%) achieving a complete response after ASCT. The 2-year progression-free survival (PFS) and overall survival (OS) rates for all patients were 46.7% (95% CI, 31.8–60.4%) and 63.7% (95% CI, 47.7–76.0%), respectively. There was no development of veno-occlusive disease and no treatment-related deaths within 100 days after ASCT. These results indicate that a BuME regimen is well-tolerated and effective for patients with relapsed or high-risk NHL, and may be comparable to some previously used regimens. This regimen may be useful as a substitute for BCNU-containing regimens.

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Introduction

Malignant lymphoma comprises 4.02% of all malignancies worldwide [1]. In Korea, lymphoid malignancy comprises 3.3% and 2.6% of all cancers in men and women, respectively [2]. While some patients respond to standard cytotoxic therapies, most patients do not. Autologous stem cell transplantation (ASCT) is superior to conventional salvage chemotherapy in patients with non-Hodgkin's lymphoma (NHL) [3]. Stiff *et al.* [4] reported that ASCT improves progression-free survival (PFS) among patients with high-intermediate or high-risk aggressive NHL who respond to induction therapy. Several high-dose therapy (HDT) conditioning regimens have been utilized for NHL; disease-free survival and overall survival (OS) rates range from 34–60% to 26–46%, respectively [5–8]. Carmustine (bis-chloroethylnitrosourea, BCNU) is an active drug used in HDT for NHL and is a major component of widely used conditioning regimens such as BCNU/etoposide/cytosine arabinoside/melphalan (BEAM) and BCNU/etoposide/cytosine arabinoside/cyclophosphamide (BEAC); however, the supply of BCNU is limited in some countries [5,9]. The introduction of intravenous busulfan as an alternative to oral busulfan renewed interest in optimizing conditioning regimens to improve treatment outcomes after allogeneic hematopoietic stem cell transplantation (SCT) for myelogenous leukemia [10,11]. Lower incidences of serious hepatic veno-occlusive disease (VOD) and other treatment-related serious adverse events are observed with intravenous busulfan compared to oral busulfan [12]. The Consortium for Improving Survival of Lymphoma (CISL) developed a protocol using intravenous busulfan, melphalan, and thiotepa (BuMT) as a conditioning regimen for HDT in patients with high-risk or relapsed NHL. However, BuMT was considered excessively toxic and the protocol was discontinued [13]. This prospectively designed clinical trial using intravenous busulfan, etoposide, and melphalan (BuME) as a conditioning regimen for HDT in patients with high-risk or relapsed NHL was developed to achieve comparable response with lower toxicity.

Methods

Patients

This prospective open-labeled, nonrandomized, multicenter phase II study was conducted at 13 centers experienced in lymphoma treatment including ASCT. Patients were enrolled from May 2009 to May 2011. Eligible patients were between 20 and 65 years of age and presented with biopsy-proven, relapsed, or primary refractory aggressive NHL that was sensitive to salvage chemotherapy, or chemosensitive high-risk NHL (two or three risk factors of the age-adjusted IPI) at diagnosis. Exclusion criteria included central nervous system (CNS) involvement of lymphoma; diagnosis of any other malignancies within the past 5 years except skin

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basal cell cancer or cervical carcinoma *in situ*; substantial impairment of cardiac, pulmonary, hepatic, or renal function; active hepatitis; known HIV-positive status; serious or uncontrolled systemic disease; pregnancy; and breast feeding. The study complied with the Declaration of Helsinki and respected the guidelines of good clinical practice. The institutional review board or ethics committee at each participating center approved the study protocol and its amendment. All patients provided written informed consent. The study was registered at ClinicalTrial.gov (NCT03792815).

Peripheral blood stem cell (PBSC) collection, cryopreservation, and infusion PBSCs were mobilized primarily with granulocyte colony-stimulating factor (G-CSF) alone or chemotherapy and G-CSF without purge. Hematopoietic stem cells (targeted number, $>3 \times 10^6$ CD34+ cells/kg) were collected from all patients using a large-volume leukapheresis apparatus of each participating institution by means of a central venous catheter. Cells were cryopreserved with dimethylsulfoxide (DMSO) to achieve a final DMSO concentration of 4.35–7.5% and stored at −80 °C. Each frozen PBSC product bag was thawed rapidly in a 40 °C water bath at the patient's bedside and infused on day 0.

Conditioning regimen

The conditioning regimen consisted of busulfan (3.2 mg/kg/day) intravenously (i.v.) on days −7, −6, and −5, etoposide (400 mg/m^2 i.v.) on days −5 and −4, and IV melphalan (50 mg/m^2/day i.v.) on days −3 and −2. The treatment was infused through a central vein catheter by means of a controlled-rate infusion pump. Phenytoin (300 mg) was administered orally during, and 1 day after, intravenous busulfan therapy, starting the evening before or on the morning of the first dose. ASCT was performed through a central line 48 h after the last dose of melphalan. Patients received care in single rooms and protocols for anti-microbiologic prophylaxis at each participating center were implanted. All patients received 5 μg/kg filgrastim or lenograstim daily, subcutaneously, beginning on day +3 until achieving an absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l for 3 days.

Clinical outcome variables

Engraftment was defined as the first of three consecutive days with ANC $\geq 0.5 \times 10^9$/l. Engraftment failure was defined as failure to engraft by day +30. Platelet engraftment was defined as the first of seven consecutive days with a platelet count of 20×10^9/l or more without transfusion support. Toxicity was scored using the modified National Cancer Institute (NCI) Common Toxicity Criteria version 3.1 (NCI, Bethesda, MD, USA). All nonhematological organ dysfunctions until day +100 post-transplantation were regarded as regimen-related toxicity and graded in accordance with the criteria of Bearman *et al.* [14].

OS was calculated from the day of transplantation, with patients alive at the time of the last administratively censored follow-up; treatment-related mortality (TRM) was defined as death due to any cause other than relapse. PFS was calculated from day 0 to relapse or disease progression.

Statistical analyses

Planned sample size was for 51 patients allowing a 10% dropout rate. Patients were recruited for 2-year accrual and 2-year minimum follow-up. The primary end point of this study was PFS at 2 years, and secondary end points included the safety and tolerability of the conditioning regimen, as well as estimation of OS. Unadjusted PFS and OS were estimated using Kaplan–Meier curves. Differences in PFS or OS between subgroups were evaluated using the log-rank test. The Cox proportional hazards regression model was used to determine whether patient characteristics were predictive of PFS and OS. A P-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS statistics (version 18.0) and EZR (version 1.33).

Results

Patient characteristics

A total of 51 patients were registered for this study. Five patients were excluded because they did not meet the eligibility criteria; three patients were primary CNS diffuse large B-cell lymphoma (DLBCL), one patient was refractory to salvage chemotherapy at the time of transplantation, and one patient had previously undergone a kidney transplantation exhibited impaired renal function (serum creatinine ≥1.5 mg/dl). Thus, 46 patients were enrolled and their data for the these were analyzed (Fig. 1). Table 1 presents the patient characteristics. A total of 34 male (74%) and 12 female (26%) patients with a median age of 51 (range, 18–64) years were included in the study. Histologic diagnoses comprised the following: B-cell NHL (n = 28, 61%), T-cell NHL (n = 13, 29%), and extranodal NK/T-cell lymphoma, nasal type (n = 5, 11%). All B-cell NHL patients received a rituximab-containing regimen as

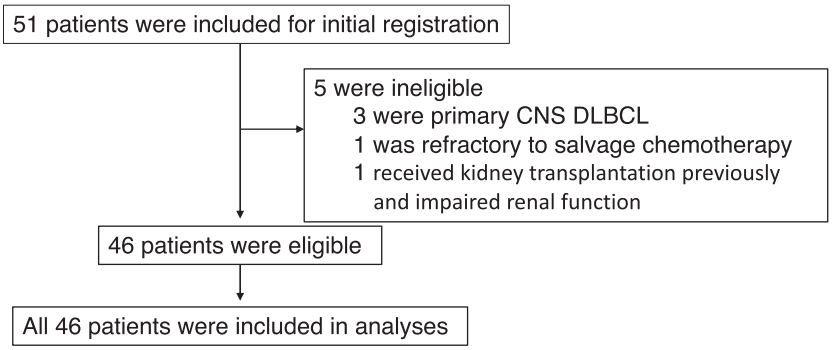

Figure 1 Kaplan–Meier curves of (a) progression-free survival and (b) overall survival after autologous stem cell transplantation for all patients (n = 46). 2-year progression-free survival rate; 46.7% (95% CI, 31.8–60.4). 2-year overall survival rate; 63.7% (95% CI, 47.7–76.0).

a first-line therapy. A total of 12 patients (26%) were at high risk for remission and received upfront ASCT, 20 patients (44%) were refractory to induction therapy but sensitive to salvage chemotherapy, and 14 patients (30%) exhibited chemosensitive relapse.

Engraftment and toxicity

The median dose of CD34+ cells transplanted was 5.35×10^6/kg (range, 1.13–77.55). All 46 patients achieved an engraftment of neutrophils (median: day 10, range, 3–30) and platelets (median: day 10, range, 2–51). There were no treatment-related deaths. Median hospitalization duration was 31 days (range, 9–80). Table 2 presents nonhematological toxicities. The most common nonhematological toxicities were mucositis (72%), nausea and vomiting (70%), and diarrhea (59%). Hepatotoxicity (39%) occurred with grade 3 intensity in 7% of patients. No VOD or cardiac toxicity was recorded within 100 days after ASCT. Although 43% of patients developed neutropenic fever, no patient deaths occurred due to infection. A total of five patients over 60 years of age and 25 patients over 50 years of age showed no significant difference in hospitalization, BM recovery, or toxicity profile.

Response and survival

A total of 36 patients (78%) achieved a complete response 1 month after ASCT, six patients had a partial response (13%), and four patients (9%) developed progressive disease. At a median follow-up of 32 months, the disease had progressed in 26 patients (57%) and 19 patients (46%) had died of the disease progression. The estimated 2-year OS and PFS rates were 63.7% (95% CI, 47.7–76.0) and 46.7% (95% CI, 31.8–60.4), respectively (Fig. 1). Upon disease progression, 17 patients (65%) received salvage treatments including chemotherapy or radiotherapy [chemotherapies (n = 9, 53%), radiotherapy (n = 5, 29%), both (n = 2, 12%), and radioimmunotherapy (n = 1, 6%)]; one patient received allogeneic hematopoietic stem cell transplantation. PFS was longer for patients with ≥2 prior chemotherapies before transplant (P = 0.052; Fig. 2). The 2-year PFS rates in patients with B-cell lymphoma (n = 28) and T-cell/NK-cell lymphoma (n = 18) were 57.1% (95% CI, 37.1–72.9) and 29.9% (95% CI, 11.0–51.7), respectively. T/NK-cell lymphoma, presence of B symptoms at diagnosis, bulky disease, and with ≥2 prior chemotherapies before transplant were identified as independent risk factors for PFS in Cox regression analyses (Figs 3 and 4; Table 3). Four patients had progressive disease in the first assessment after ASCT; two patients exhibited DLBCL, and the other two exhibited PTCL, NOS, and ALCL.

Discussion

The most frequently used HDTs for NHL are those based on a BCNU backbone: BEAM, BEAC, and cyclophosphamide/BCNU/etoposide [5,9,15]. Drugs such as cytosine arabinoside (Ara-C), BCNU, daunorubicin, and thiotepa are increasingly in short supply, affecting patients with hematological malignancies including leukemia and lymphoma. Because the supply of BCNU is limited in Korea, busulfan often replaces BCNU in conditioning regimens for several lymphomas [16]. This multicenter, prospective phase II trial assessed the efficacy and safety of a BuME regimen as conditioning for HDT in patients with high-risk or relapsed NHL. The 2-year PFS and OS rates were 46.2% and 63.7%, respectively. In the SWOG 9704 trial, which evaluated the efficacy of ASCT during the first remission in patients with NHL, the 2-year PFS and OS rates

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Table 1. Patient characteristics.

Characteristic	Number of patients (n = 46) No. %
Age (years)	
Median (range)	51 (18–64)
>60 years of age at ASCT	5 (11%)
Gender	
Male	34 (74)
Female	12 (26)
Histologic subtype	
Diffuse large B-cell lymphoma	25 (54)
Mantle cell lymphoma	3(6)
Extranodal NK/T-cell lymphoma, nasal type	5 (11)
Angioimmunoblastic T-cell lymphoma	4 (9)
Anaplastic large cell lymphoma (ALK-)	4 (9)
Peripheral T-cell lymphoma, unspecified	5 (11)
Ann Arbor stage at diagnosis	
1	4 (9)
2	8 (17)
3	12 (26)
4	22 (48)
B symptoms at diagnosis	13 (28)
IPI at diagnosis	
Low (0–1)	11 (24)
Low-intermediate (2)	14 (30)
High-intermediate (3)	17 (37)
High (4–5)	4 (9)
BM involvement	9 (20)
Extranodal involvement at diagnosis	29 (63)
Median time from diagnosis to ASCT (months)	9.6 (3.3–62.8)
Status at transplantation	
High risk in remission (upfront ASCT)	12 (26)
Refractory to induction therapies	20 (44)
Chemosensitive relapsed	14 (30)
Number of prior chemotherapy regimens	
1	19(41)
2	24 (52)
≥3	3(7)
Response status at transplantation	
CR	23 (50)
No CR	23 (50)
CD 34+ cell infused, $\times 10^6$ kg	
Median number (range)	5.35 (1.13–775)

were 69% and 74%, respectively, for the upfront ASCT group. Only 11% of the T-cell lymphomas were included in that study [4]. Compared to aggressive B-cell lymphomas, the prognosis for aggressive T-cell lymphomas is generally poor [17,18] and our results were consistent. In this study, there was a significantly higher number of T-cell lymphoma/NK-T-cell lymphoma (n = 18, 40%) cases in this study compared to the SWOG 9704 trial. Upfront ASCT was present in 26% (12/46 patients) of study participants; 50% (23/46 patients) of patients did not achieve a complete response before transplantation. The BuME regimen demonstrated promising efficacy despite the inclusion of many subtypes of NHL with poor prognoses, with 78.3% post-transplantation CR and 2-year PFS of 46.2%. Survival outcomes between BuME and other conditioning regimens such as BEAM and BuCE could not be compared because this study had a single-arm design. Other studies have reported outcomes of conditioning regimens that are commonly employed in routine clinical practice[16]. Kim *et al.* [19] reported a median event-free survival durations of 16.1 months (95% CI: 0.0–53.5 months) in a BEAM group and 11.3 months (95% CI, 0.0–29.9 months) in a BuCE group. Our results are at least equivalent to those of other published regimens.

The greatest disadvantage of transplantation compared to conventional chemotherapy is the incidence of transplant-related mortality [20]. This new regimen has been proposed to reduce toxicity, procedure cost, and hospital stay duration, without compromising the quality of life and survival of patients [21,22]. Busulfan has been extensively utilized in autologous and allogeneic transplantation for a variety of lymphohematopoietic disorders [20]. Busulfan and cyclophosphamide (BuCy) was initially evaluated as a preparative of HDC for NHL [23]. Severe VOD is the most common life-threatening toxicity of the BuCy regimen, and high-dose cyclophosphamide may result in specific toxicities including hemorrhagic cystitis and cardiac toxicity. Revised conditioning regimens were evaluated, including lowering the dose of busulfan and/or adding other medications such as etoposide. The incidence of severe VOD was reduced by 3–10% [20,24]. A protocol using intravenous busulfan, melphalan, and thiotepa as a conditioning regimen for HDT in patients with high-risk or relapsed NHL was previously developed. The efficacy of this regimen was notable, but grade 3–4 mucositis and liver toxicity occurred in 69.2% (9/13 patients) of patients and VOD in 46% (6/13 patients) of patients [13]. Regimens with triple alkylating drugs may contribute to such toxicities. There were no cases of VOD in this study. Pulmonary toxicity was observed in 2% of patients. Common early toxicities in this study were diarrhea, mucositis, and nausea/vomiting. These were associated with mucosal damage and diminished after bone marrow recovery. No transplant-related deaths occurred during this study, and no Gr3/Gr4 cardiotoxicities were observed. Cardiotoxicity is often a complication related to high-dose cyclophosphamide [25–27]. In

Table 2. Nonhematological toxicities.

	All patients (n = 46)		
	All grade No. (%)	Gr 1 and 2 toxicities No. (%)	Gr 3 and 4 toxicities No. (%)
Any adverse event			
Toxicities			
Fever without documented organism	26 (57)		
Fever with documented organism	2 (4)		
Mucositis	33 (72)	27 (59)	6 (13)
Nausea/vomiting	32 (70)	30 (65)	2 (4)
Diarrhea	27 (59)	23 (50)	4 (9)
Hepatic toxicities	18 (39)	15 (33)	3 (7)
Skin	2 (4)	2 (4)	0 (0)
Bladder	2 (4)	2 (4)	0 (0)
Pulmonary	1 (2)	1 (2)	0 (0)
Renal toxicity	1 (2)	0 (0)	1 (2)
Peripheral neuropathy	1 (2)	1 (2)	0 (0)
Veno-occlusive disease	0 (0)	0 (0)	0 (0)
Cardiac toxicity	0 (0)	0 (0)	0 (0)
CNS	0 (0)	0 (0)	0 (0)
Allergy	0 (0)	0 (0)	0 (0)
Death			
Treatment-related death	0 (0)		

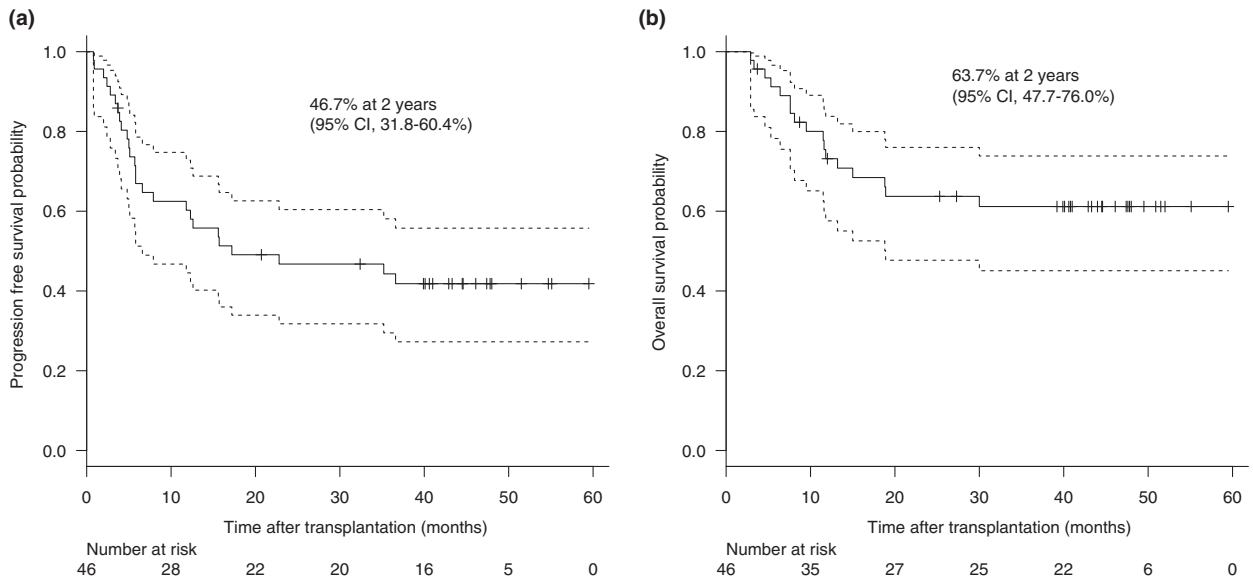

Figure 2 (a) Progression-free survival and (b) overall survival according to number of prior chemotherapy regimens, 2-year progression-free survival rate; 61.3% (95% CI, 35.5–79.3) vs. 41.7% (95% CI, 22.2–60.1) vs. NA in 1 vs. 2 vs. 3 (P = 0.021). 2-year overall survival rate; 82.9% (95% CI, 55.7–94.2) vs. 52.9% (95% CI, 31.2–70.6) vs. 33.3% (95% CI, 9–77.4) in 1 vs. 2 vs. 3 (P = 0.095).

Korea, a BuCE conditioning regimen is commonly used with ASCT to treat lymphoma with a high-dose cyclophosphamide-containing regimen [8]. Patients with lymphoma commonly receive anthracycline-containing chemotherapies prior to ASCT. Kuitttinen *et al.* [28] indicated that high-dose cyclophosphamide results in acute, subclinical systolic LV dysfunction in NHL patients previously treated with anthracyclines. Rituximab-related cardiotoxicity in the form of cardiac arrhythmia occurs at a frequency of 8% [29]. Patients

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Table 3. Multivariable analysis of progression-free survival.

	PFS		
Category	HR	95% CI	*P*
Histology			
B-cell lymphoma	1		0.033
T/NK-cell lymphoma	2.683	1.083–6.644	
B symptoms at diagnosis			
No	1		0.026
Yes	2.862	1.137–7.203	
Bulky disease			
No	1		0.026
Yes	6.960	1.263–38.360	
Number of prior chemotherapy regimens			
1	1		0.043
≥2	2.715	1.031–7.147	

receiving ASCT are often at an increased risk for cardiotoxicity, even if their cardiac function is normal. BEAC is generally a more toxic regimen for cardiotoxicity than BEAM, due to the differences between cyclophosphamide and melphalan [28,30]. Omitting high-dose cyclophosphamide in ASCT may be an important advance in terms of safety. A BuME regimen has demonstrated favorable toxicity profiles in nonhematological and hematological toxicities. Rapid neutrophil (median: day 10, range, 3–30) and platelet (median: day 10, range, 2–51) engraftment was observed; 65% (17 of 26) patients could receive salvage treatment after relapse. The BuME conditioning regimen was well tolerated for the toxicities of concern.

The present study has several limitations. First, this study was phase II trial that included a small number of patients and was nonrandomized. Second, the clinical features and prognosis of lymphoma vary according to histologic types; therefore, a study regarding transplantation with one tissue type is required. In addition, the clinical setting of patients in this study was overly diverse due to broad inclusion criteria. Frontline consolidation, sensitive relapsed, and refractory patients were included, and there was a difference in tumor burden at the time of transplantation. Thus, it is difficult to define the most appropriate role of BuME as a conditioning regimen for HDT in patients with non-Hodgkin's lymphoma. Nevertheless, this study is the first to report the results of a BuME regimen and showed that further studies are warranted.

In conclusion, a BuME conditioning regimen prior to ASCT was a well-tolerated and effective treatment for high-risk or relapsed NHL. This regimen may be an important treatment option as a substitute for BCNU-containing regimens. The randomized trial including the BuME regimen is currently ongoing.

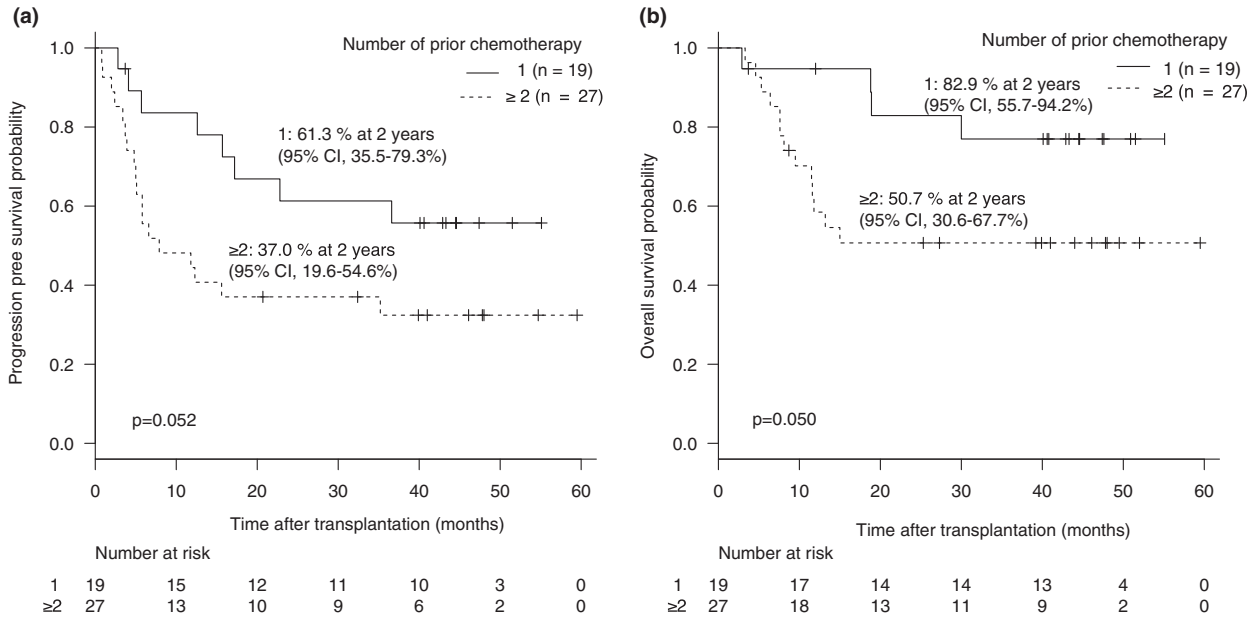

Figure 3 (a) Progression-free survival and (b) overall survival according to histologic type (B-cell lymphoma vs T/NK-cell lymphomas). 2-year progression-free survival rate; 57.1% (95% CI, 37.1–72.9) vs. 29.9% (95% CI, 11.0–51.7), in B-cell lymphoma vs. T/NK-cell lymphoma ($P = 0.182$). 2-year overall survival rate; 63.4% (95% CI, 42.6–78.4) vs. 64.2% (95% CI, 36.8–82.2) in B-cell lymphoma vs. T/NK-cell lymphoma ($P = 0.676$).

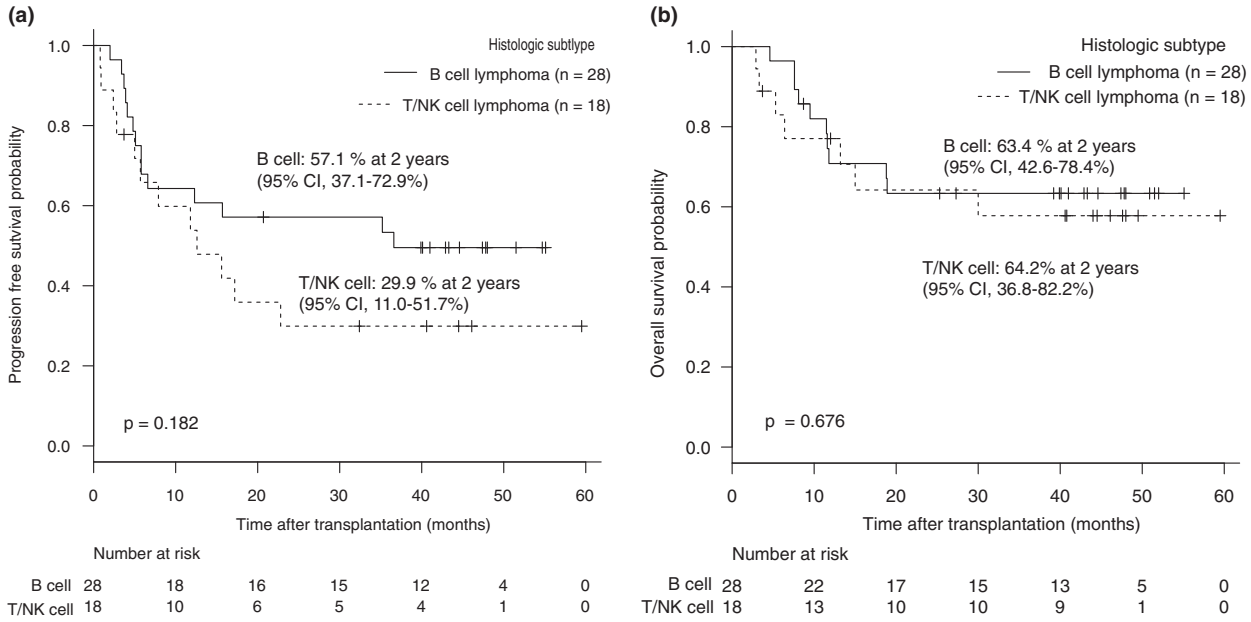

Figure 4 (a) Progression free survival and (b) Overall survival according to histologic type B cell lymphoma (n = 28) and T/NK cell lymphoma (n = 18).

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Conflict of interest

The authors declare that they have no conflict of interest.

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