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Autologous

High-Dose Chemotherapy with Autologous Stem Cell Transplantation in Primary Central Nervous System Lymphoma: Data From the Japan Society for Hematopoietic Cell Transplantation Registry

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A B S T R A C T

High-dose chemotherapy (HDT) with autologous stem cell transplantation (ASCT) has been shown to improve the prognosis of patients with central nervous system (CNS) lymphoma. We queried the Japan Society for Hematopoietic Cell Transplantation Registry for 2006 to 2015 to analyze the outcomes of 102 patients with primary CNS lymphoma (PCNSL) who underwent first HDT/ASCT. The median patient age was 54 years (range, 20 to 74 years), and 65 patients were treated in an upfront setting. With a median duration of follow-up of 44 months, the 5-year overall survival (OS) and progression-free survival (PFS) were 54.9% and 38.4%, respectively. There were no significant differences in OS and PFS between upfront and salvage HDT/ASCT. Because thiotepa, a key agent in HDT/ASCT for PCNSL, has been unavailable since 2011 in Japan, the HDT regimens used were not uniform. Thiotepa-containing HDT was received by 16 out of 32 patients before 2010, but by only 2 of 70 patients after 2011. Thiotepa-containing HDT was associated with better PFS ($P = .019$), lower relapse ($P = .042$), and a trend toward a survival benefit. In multivariate analysis, noncomplete remission at HDT/ASCT was an independent predictor for OS (hazard ratio [HR], 2.40; 95% confidence interval [CI], 1.25 to 4.58; $P = .008$) and thiotepa-containing HDT remained significant for PFS (HR, .42; 95% CI, .19 to .95; $P = .038$). These results confirm the activity of thiotepa-containing regimens.

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INTRODUCTION

Primary central nervous system (CNS) lymphoma (PCNSL) is a rare aggressive extranodal lymphoma accounting for only 4% of primary brain tumors and 1% to 2% of cases of non-Hodgkin lymphoma in Japan [1]. The incidence has been increasing in recent years, especially in the immunocompetent and elderly population in both Japan [2,3] and Western countries [4]. Because of the rarity of PCNSL and the reduced capacity of drugs to cross the blood-brain barrier (BBB), the standard of care has not been firmly established, but induction therapy with a high-dose methotrexate-based regimen is a widely

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accepted treatment strategy for newly diagnosed PCNSL. Although whole-brain irradiation (WBRT) is effective in disease control and has been historically used as consolidation therapy in PCNSL, WBRT is often avoided owing to its potential delayed neurotoxicity [5]. High-dose chemotherapy (HDT) with autologous stem cell transplantation (ASCT) has been reported as a promising approach in multiple studies [4,6] and is another option for consolidation therapy in PCNSL.

Commonly used HDT regimens in patients with PCNSL are thiotepa-based regimens, carmustine (BCNU)-thiotepa [7–10], and thiotepa-busulfan-cyclophosphamide (TBC) [11–14]. Thiotepa and BCNU are currently unavailable in Japan. Although thiotepa had been used for many decades in Japan, the supply was discontinued in 2009 when the active ingredient went out of production, and the final manufacturing of thiotepa in Japan ended 2010. In HDT/ASCT for relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), other HDT regimens than BEAM, such as MCEC (ranimustine [MCNU], carboplatin, etoposide, cyclophosphamide) [15], LEED (melphalan, etoposide, cyclophosphamide, dexamethasone) [16], and MEAM (BEAM modified regimen using MCNU) [17] has been developed in Japan. In HDT/ASCT for PCNSL, especially after 2011, patients have been treated with various HDT regimens without thiotepa.

The purpose of this retrospective study based on the Japan Society for Hematopoietic Cell Transplantation (JSHCT) registry database was to provide the outcomes of HDT/ASCT in patients with PCNSL in Japan and to investigate the role of each chemotherapeutic agent in HDT regimens.

METHODS

Study Design and Data Collection

We retrospectively analyzed clinical data collected through the Transplant Registry Unified Management Program (TRUMP) sponsored by the JSHCT and the Japanese Data Center for Hematopoietic Cell Transplantation [18,19]. The TRUMP collects pretreatment patient characteristics and renews data on survival and disease status annually using follow-up forms. The inclusion criteria in this retrospective analysis included patients with PCNSL who received a first HDT/ASCT between 2006 and 2015. The Institutional Review Board of the Kawasaki Medical School Hospital, where this study was carried out, approved this retrospective study.

Endpoints and Definitions

The primary outcomes were progression-free survival (PFS) and overall survival (OS); secondary endpoints were transplantation-related mortality (TRM) and identification of clinical and biological features that may influence the outcomes of HDT/ASCT. OS was defined as the time from transplantation to death or latest follow-up. PFS was defined as the time from transplantation to relapse/progression or death from any cause or latest follow-up. TRM was defined as mortality from any cause other than disease progression.

Statistical Analysis

Differences in distribution of clinical characteristics between groups were analyzed with the Fisher exact test or Mann-Whitney *U* test. Survival curves were calculated using the Kaplan-Meier product limit estimate [20], groups were compared using the log-rank test, and risk factor analysis was done using a Cox regression model [21]. Two-group analysis of the cumulative incidence of relapse was conducted using the Gray test. Factors were analyzed in univariable analysis, and all factors with $P \leq .1$ were retained in the multivariable model. All *P* values were 2-sided, and $P < .05$ was considered to indicate statistical significance. All statistical analyses were performed with Stata version 12.1 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

A total of 102 patients with PCNSL who were treated with HDT/ASCT between 2006 and 2015 were identified in the JSHCT registry. Baseline characteristics at the time of diagnosis and before HDT-ASCT are summarized in Table 1. Among the 102 patients, 65 received HDT/ASCT in an upfront setting and 37 received HDT/ASCT in a salvage setting. Median patient age was 54 years (range, 20 to 74 years) at the time of HDT/ASCT, with 15 patients age >64 years. The majority of patients (77%) had previously received rituximab, but details on induction or salvage chemotherapies were not recorded in the registry. The Memorial Sloan–Kettering Cancer Center (MSKCC) and International Extranodal Lymphoma Study Group (IELSG) prognostic score [22,23] could not be calculated, because Karnofsky Performance Score and cerebrospinal fluid (CSF) protein concentration at diagnosis were not collected. All variables other than time from diagnosis to ASCT did not differ between the upfront and salvage groups (Table 1).

HDT Regimens

The various HDT regimens were used are listed in Table 1, and details are provided in Supplementary Table S1. One-half of the patients (16 of 32 patients) received thiotepa-containing HDT regimens before 2010; however, almost all patients (70 of 72; 97.2%) received HDT regimens without thiotepa after 2011 owing to the unavailability of thiotepa in Japan. Because BCNU also is not available in Japan, other nitrosourea agents, MCNU and rarely nimustine (ACNU), served as an alternative. In the thiotepa-containing HDT group (n = 18), 9 patients received TBC (thiotepa + busulfan + cyclophosphamide) [11-14] and 7 received BuTT (busulfan + thiotepa) [24]. In the HDT without thiotepa group (n = 84), approximately one-half of the patients received a common HDT regimen for r/r DLBCL in Japan [25]. In detail, 24 patients received a modified BEAM regimen (MEAM; ranimustine instead of carmustine + etoposide + cytarabine + melphalan) [17,26], 10 patients received LEED (melphalan + etoposide + cyclophosphamide + dexamethasone) [16,27,28] and 9 patients received MCEC (ranimustine + carboplatin + etoposide + cyclophosphamide) [15,26]. Rituximab was also administered to 24 patients in the HDT without thiotepa group but to no patients in the thiotepa-containing HDT group (Supplementary Table S2). Planned WBRT following HDT/ASCT was performed in 3 patients.

Treatment Response and Survival after HDT/ASCT

The median number of reinfused $CD34^+$ hematopoietic stem cells was 3.2×10^6/kg (range, 1.1 to 42.2×10^6/kg). All patients engrafted, with a median time to an absolute neutrophil count $\geq 500/mm^3$ of 10 days (range, 8 to 20 days). The platelet count recovered to $>50{,}000/mm^3$ at a median of 17 days (range 9 to 108 days) in 94 of 102 patients (92.2%). Response status before and after HDT-ASCT is summarized in Table 2. Following HDT/ASCT, 20 of 31 patients who were not in CR at the time of HDT/ASCT achieved CR; thus, 91 of 102 patients (89.2%) were in CR after HDT/ASCT. Sixty-three of the 102 patients (62%) were alive at a median follow-up of 44 months. Median OS was not reached, and median PFS was 18.7 months (95% confidence interval [CI], 9.5 to 30.4 months). The 2-year and 5-year OS were 72.1% (95% CI, 61.8% to 79.9%) and 54.9% (95% CI, 42.9% to 65.5%), respectively, and the 2-year and 5-year PFS were 45.0% (95% CI, 35.0% to 54.5%) and 38.4% (95% CI, 28.5% to 48.2%), respectively (Figure 1). OS and PFS did not differ significantly between the patients who underwent HDT/ASCT in an upfront setting and those who did so in the salvage setting (5-year OS, 55.7% versus 54.7%, respectively [$P = .36$]; 5-year PFS, 41.4% versus 33.0%, respectively [$P = .20$]) (Figure 2). Survival associated with each HDT regimen is shown in Supplementary Figure S1.

Because thiotepa-based HDT regimens, such as BCNU-thiotepa and TBC, are common in Europe and the United States, outcomes were compared between the patients receiving thiotepa-containing HDT and those receiving HDT without

Table 1
Patient Characteristics

Characteristic	Total (N = 102)	HDT/ASCT in Upfront Setting (N = 65)	HDT/ASCT in Salvage Setting (N = 37)	*P* Value
Age at ASCT, yr, median (range)	54 (20-74)	54 (20-74)	54 (32-67)	.80
Time from diagnosis to ASCT, mo median (range)	7 (3-112)	6 (3-12)	28 (6-112)	<.001
Sex, n				
Female	38	23	15	.67
Male	64	42	22	
ECOG-PS at diagnosis, n				
0-1	86	54	32	.78
2-4	16	11	5	
LDH at diagnosis, n				
Elevated	17	13	4	.28
Not elevated	85	52	33	
Rituximab in induction/salvage, n				
Yes	77	52	25	.27
No	3	2	1	
Unknown	22	11	11	
Remission before HDT-ASCT, n				
CR	71	48	23	.002
PR	21	14	7	
SD/PD	7	0	7	
Unknown	3	3	0	
HDT regimen, n				
MEAM*	24	13	11	
BuMel	10	6	4	
LEED*	10	6	4	
MCEC*	9	8	1	
TBC†	9	4	5	
BuCy	7	6	1	
BuTT†	7	5	2	
BuCyE	4	3	1	
Others	22	14	8	
Rituximab addition in HDT, n				
Yes	24	16	8	.81
No	78	49	29	
Planned WBRT following HDT/ASCT, n				
Yes	3	2	1	.66
No	99	71	28	
Year of HDT/ASCT, n				
2006-2010	32	21	11	.83
2011-2015	70	44	26	

MEAM indicates MCNU + etoposide + cytarabine + melphalan; BuMel, busulfan + melphalan; LEED, melphalan + etoposide + cyclophosphamide + dexamethasone; MCEC, MCNU + calboplatin + etoposide + cyclophosphamide; TBC, thiotepa + busulfan + cyclophosphamide; BuCy, busulfan + cyclophosphamide; BuTT, busulfan + thiotepa; BuCyE, busulfan + cyclophosphamide + etoposide.

* Commonly used HDT regimens in relapsed/refractory DLBCL in Japan.

† Thiotepa-containing HDT regimen.

thiotepa. Among the variables considered, only the year of transplantation and rituximab use in induction or salvage therapy and the treatment response after HDT/ASCT differed between the 2 groups (Supplementary Tables S2 and S3). The patients treated with thiotepa-containing HDT (n = 18) had a significantly better 5-year PFS (65.7% versus 31.8%; *P* = .019) and showed a trend toward better 5-year OS (69.1% versus 52.1%; *P* = .14) (Figure 3A and B).

Among the patients who achieved CR after HDT/ASCT, the cumulative incidence of relapse (CIR) was significantly lower in the thiotepa-containing HDT group compared with the HDT without thiotepa group (2-year CIR, 27.8% versus 57.3%, *P* = .042) (Figure 3C). In the thiotepa-containing HDT group, there was no significant difference in OS and PFS between the patients who received TBC and those who received BuTT (*P* = .57 for OS, *P* = .35 for PFS) (Supplementary Figure S1). Results of univariate and multivariate analyses of the risk factors for OS and PFS are summarized in Table 3. Multivariate analysis identified non-CR at HDT/ASCT as an independent prognostic factor for worse OS (HR, 2.40; 95% CI, 1.25 to 4.58;

Table 2
Best Response after HDT/ASCT

Response Status after HDT/ASCT	Response Status before HDT/ASCT					
	In Upfront Setting		In Salvage Setting			
	CR (n = 50)	PR (n = 15)	CR (n = 21)	PR (n = 6)	SD/PD (n = 7)	Unknown (n = 3)
CR	50	9*	21	3*	6*	2*
PR		6		3		
SD/PD					1	1

* These patients achieved CR after HDT/ASCT.

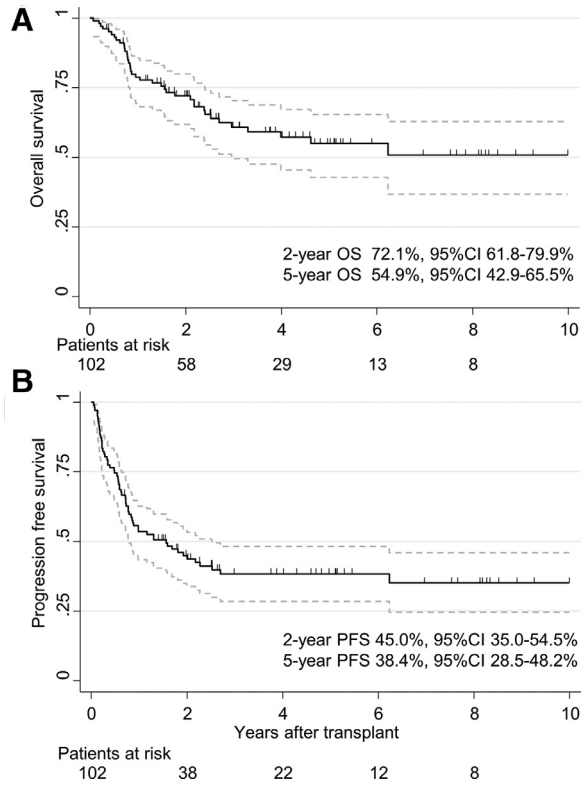

Figure 1. OS (A) and PFS (B) from the time of HDT/ASCT.

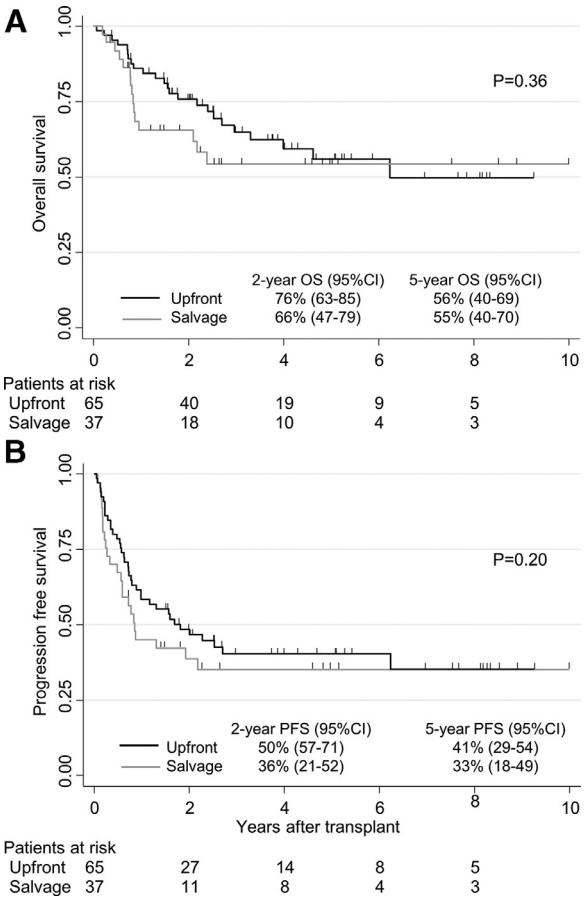

Figure 2. OS (A) and PFS (B) in HDT/ASCT upfront setting (black lines) or as salvage therapy (gray lines).

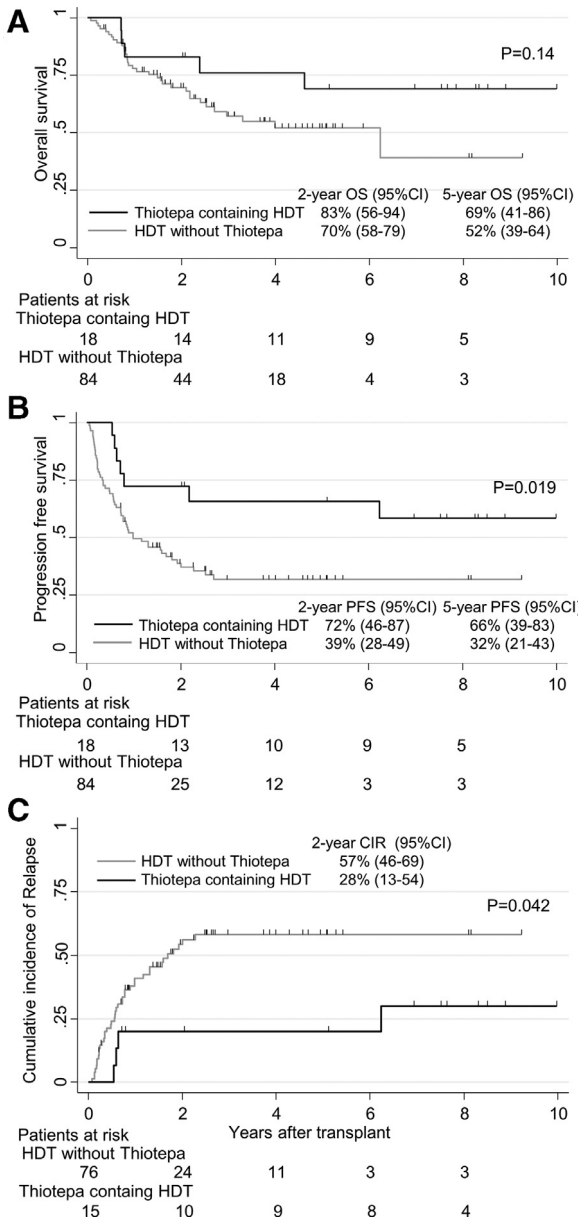

Figure 3. OS (A) and PFS (B) of all patients (n = 102) and cumulative incidence of relapse (CIR) of patients in CR after HDT/ASCT (C; n = 91) for patients receiving thiotepa-containing HDT (black lines) or HDT without thiotepa (gray lines).

P = .008) and thiotepa use in HDT as an independent prognostic factor for better PFS (HR, .42; 95% CI, .19 to .95; *P* = .038).

Toxicity of HDT/ASCT and Nonrelapse Mortality

Seven of the 102 patients (6.9%) died without disease progression. Two of these 7 died within 100 days of ASCT, 1 from infection with an unknown pathogen (on day 81) at age 49 years and 1 from sepsis (on day 98) age 61 years. Both of these patients had been treated with a BuMel (busulfan + melphalan) regimen. In the other 5 patients, 1 died from acute respiratory distress syndrome at age 51 years, 1 died from idiopathic interstitial pneumonia at age 53 years, 1 died from bacterial infection at 60 years, 1 died from respiratory failure at 61 years, and 1 died from an unknown cause at 69 years. Two of these patients were treated with ACNU-thiotepa, 1 was treated with BuTT, 1 was treated with MEAM, and 1 was treated with MCEC.

Table 3
Univariate and Multivariate Cox Regression Analysis of Prognostic Factors

Outcome/Factor	OS						PFS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age ≥60 yr	1.7	.9-3.2	.1	1.85	.98-3.52	.06	1.45	.87-2.42	.16			
Female sex	.61	.31-1.2	.15				.71	.42-1.21	.21			
Elevated LDH	1.42	.65-3.1	.38				1.84	.99-3.42	.05	1.62	.87-3.01	.13
ECOG-PS ≥2	1.21	.53-2.73	.66				.87	.43-1.77	.7			
Non-CR	2.23	1.17-4.25	.02	2.4	1.25-4.58	.01	1.28	.74-2.21	.37			
Salvage	1.07	.53-2.15	.86				1.3	.76-2.24	.34			
Thiotepa-containing HDT	.49	.19-1.28	.15				.39	.18-.88	.02	.42	.19-.95	.04
Busulfan-containing HDT	.77	.4-1.48	.44				1.07	.64-1.77	.8			
Cyclophosphamide-containing HDT	.91	.48-1.71	.77				1.03	.62-1.71	.91			
Nitrosourea-containing HDT	1.35	.72-2.54	.35				.99	.59-1.64	.96			
Cytarabine-containing HDT	.75	.36-1.6	.46				.76	.43-1.37	.37			
Etoposide-containing HDT	.92	.49-1.75	.81				.92	.55-1.53	.75			
Rituximab-containing HDT	1.53	.76-3.09	.24				1.42	.8-2.52	.23			

DISCUSSION

This retrospective study is the first large series to report outcomes following HDT/ASCT in patients with PCNSL in Japan. Numerous retrospective [6,29,30] and prospective [8,11,13,31] studies in Europe and the United States have demonstrated the feasibility and efficacy of HDT/ASCT as consolidation therapy for patients with PCNSL. HDT/ASCT can also be effective in patients with relapsed or refractory PCNSL [7,32], even after first-line HDT/ASCT [33]. Although the HDT regimen in PCNSL consisted of agents with excellent CNS penetration, such as thiotepa, busulfan, and BCNU [6,34], various HDT regimens including the same regimens as used for r/r DLBCL were used in this study owing to the unavailability of thiotepa in Japan after 2011. The OS in this study was encouraging (median not reached; 2-year OS, 72.1%); however, the PFS (median, 18.7 months; 2-year PFS, 45.0%) seemed to be inferior to values reported in previous studies. This might be related to the fact that approximately one-half of the patients received HDT without thiotepa relapsed within 2 years after ASCT.

The reported results for the BEAM regimen, the most common HDT regimen for r/r DLBCL, in patients with PCNSL were disappointing [35,36]. In the Phase II trial addressing BEAM-conditioned ASCT [35], the median event-free survival was 9 months, and the 2-year OS was 60%. Of note, 57% of patients who underwent ASCT experienced relapse within the first 6 months of follow-up. These results may be explained by the poor CNS penetration capability of the agents other than BCNU in the BEAM regimen, including 5% for etoposide, 6% to 22% for cytarabine, and 10% for melphalan [6,34]. Owing to the unavailability of BCNU in Japan, modified BEAM (MEAM) [17], LEED [16], and MCEC [15] are commonly used HDT regimens for r/r DLBCL [25]. Two small series (n = 6 and 7) of HDT/ASCT with LEED for patients with PCNSL [27,28] have shown a favorable OS (76.2% and 85% at 2 years) and a low relapse rate (1 of 6 and 2 of 7). In the present study, the OS of patients who received LEED was comparable to those reported previously (2-year OS, 90%; n = 10), but the relapse rate was higher (40%; 2-year PFS, 47.3%) (Supplementary Figure 1). The BEAM regimen is generally not recommended in patients with PCNSL [6] but might be suitable for the other common HDT regimens for r/r DLBCL.

Busulfan also has excellent CNS penetration [34], but busulfan itself has not been associated with improved survival in this study [31]. Most of the patients (16 of 18 patients) in the thiotepa-containing HDT group received busulfan in combination with thiotepa (TBC, n = 9; BuTT, n = 7), and this group had an overall favorable prognosis. However, PFS was poor (median, 6.7 months) in the patients who received busulfan-containing thiotepa-noncontaining HDT regimens, such as BuCyE, BuMel, and BuCy (Supplementary Figure S1). This is consistent with the high relapse rate (6 of 11 patients) in a previous retrospective study of a BuCyE regimen in patients with PCSNL [37]. Thiotepa might not be substitutable in HDT regimens to treat PCNSL. As shown in the ongoing IELSG-32 study, a thiotepa-containing regimen (MATRix; methotrexate-cytarabine-rituximab combination plus a regular thiotepa dose of 30 mg/m^2) has also been effective in induction chemotherapy [9]. In the IELSG-43 study, patients with PCNSL are treated with MATRix during induction and then randomized to high-dose thiotepa-containing HDT/ASCT or conventional-dose chemotherapy (R-DeVIC; rituximab, dexamethasone, ifosfamide, and cytrabine) during consolidation [38]. The IELSG-43 study aims to clarify whether thiotepa is required during both induction and consolidation.

Toxicity, including TRM, is an important issue in HDT/ASCT. The 100-day TRM of 2.0% and long-term TRM of 6.9% in this study were not higher than values reported in previous studies [6,29]. Whereas the TBC regimen is reportedly associated with a higher TRM (13% to 14%) [11,39], no patient who received the TBC regimen in this study died of TRM. The TBC regimen, consisting of thiotepa (250 mg/m^2 for 3 days), busulfan (3.2 mg/kg for 3 days), and cyclophosphamide (60 mg/kg for 2 days) [11], is a highly intensive regimen that has been associated with higher incidences of autologous GVHD (14%) [40], viremia (35%), and fungal infections [41]. The authors noted these risks of the TBC regimen and discussed modifications of the TBC regimen to reduce its toxicity and safety profile [41].

The median age at presentation of patients with PCNSL is 65 to 69 years [1,42] and the incidence in individuals age >65 years is significantly higher than that in the general population (1.6%/year) [42]. Because elderly patients are at increased risk for neurologic toxicity after WBRT [5], age eligibility is an important issue for HDT/ASCT in PCNSL. The upper age limit for HDT/ASCT in r/r DLBCL, once 65 years, is now >65 years in clinical practice as long as all other eligibility criteria are met [43–45]. In the 2 prospective studies for HDT/ASCT in PCNSL, patients up to age 70 years (IELSG-32) [31] or 72 years (MSKCC) [11] were eligible. In the European Group for Blood and Marrow Transplantation registry data, HDT/ASCT had a favorable outcome (2-year PFS, 62.0%; 2-year OS, 70.8%)

in 52 patients with PCNSL age ≥65 years (range, 65 to 77 years), and the study concluded that HDT-ASCT using a thiotepa-based conditioning regimen was feasible and effective in selected elderly patients with PCNSL [30]. This study included 15 patients age ≥65 years at the time of HDT/ASCT (range, 65 to 74 years). At the conclusion of the study, 7 of the 15 patients were alive, and 3 had not experienced relapse. As for r/r DLBCL, older age (>65 years) itself should not be a contraindication for HDT/ASCT in PCNSL as long as other eligibility criteria are met.

Two recent trials compared HDT/ASCT and WBRT as consolidation therapy for PCNSL (IELSG-32 and PRECIS [ClinicalTrials.gov identifier NCT00863460]) In the second randomization of the IELSG-32 study, there was no difference in survival between HDT/ASCT and WBRT recipients (2-year PFS, 69% versus 80%; $P = .17$), but WBRT was associated with potential impairment of specific cognitive functions [31]. In the preliminary results of the PRECIS study, 2-year PFS was higher in the HDT/ASCT group compared with the WBRT group (86.8% versus 63.2%), and 2-year OS was 86% in both treatment groups. The neuropsychological assessment data in the PRECIS study is scheduled to be reported after prospective evaluation [46]. The use of novel agents, such as BTK inhibitor [47], PI3K inhibitor, immunomodulatory drugs [48,49], and anti PD-1 antibody [50], has shown promising results in the treatment of r/r PCNSL [51]. These agents are currently being evaluated both as single-agent therapy and in combination with other agents in clinical trials. Incorporation of novel agents into the treatment in PCNSL can help improve outcomes in patients with PCNSL, especially those ineligible for HDT/ASCT.

In conclusion, our data on the long-term outcomes of patients with PCNSL treated with HDT/ASCT in Japan suggest that HDT/ASCT is an effective and feasible strategy with acceptable mortality for eligible patients with PCNSL, and that thiotepa-containing HDT might be advantageous, especially for disease control. CR status at HDT/ASCT and thiotepa use in HDT regimens were identified as independent prognostic predictors for OS and PFS, respectively. Currently, a pharmaceutical company is redeveloping thiotepa with the goal of securing new approval for HDT/ASCT in pediatric solid cancers and adult lymphoma in Japan (JapicCTI-163433). Further evaluation of thiotepa in prospective clinical trials is warranted.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.01.020.

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