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ORIGINAL ARTICLE

Thiotepa, busulfan, and cyclophosphamide or busulfan, cyclophosphamide, and etoposide high-dose chemotherapy followed by autologous stem cell transplantation for consolidation of primary central nervous system lymphoma

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Abstract

Primary central nervous system lymphoma (PCNSL) is a rare extranodal non-Hodgkin lymphoma for which standard treatment has yet to be established. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is a suitable consolidation strategy for patients who respond to induction chemotherapy. The purpose of this study was to compare the outcome and toxicity profile of the combination of busulfan, cyclophosphamide, and etoposide (BuCyE) with that of the combination of thiotepa, busulfan, and cyclophosphamide (TBC) as conditioning regimens of upfront ASCT for consolidation therapy in PCNSL. The PCNSL registry data set, prospectively collected from March 1993 to May 2017 at Asan Medical Center, was reviewed retrospectively. Patients with objective response to induction chemotherapy who received BuCyE or TBC as conditioning regimen for ASCT were included in the analysis. Primary endpoints were overall survival (OS) and progression-free survival (PFS). Among 241 patients with a diagnosis of PCNSL, 53 received ASCT as upfront consolidation therapy with TBC (28 patients) or BuCyE (25 patients) as conditioning regimen. No median OS or PFS was reached in the TBC group, while the BuCyE group reached a median OS of 4.9 years ($p = 0.02$) and median PFS of 1.1 years ($p = 0.007$). The incidence of oral mucositis, nausea, and vomiting was higher with TBC than BuCyE. The median admission duration and days to engraftment were similar between the two groups. Despite the greater incidence of adverse events, TBC showed better outcomes than BuCyE in terms of survival.

Keywords Primary central nervous system lymphoma · Consolidation · Autologous stem cell transplantation · Thiotepa · Busulfan · Cyclophosphamide · Etoposide

Jaewon Hyung and Jung Yong Hong contributed equally to this study as co-first authors.

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare extranodal non-Hodgkin lymphoma (NHL) comprising only 2% of the primary central nervous system tumor cases in the USA [1]. PCNSL involves the brain, the leptomeninges, the eye, or the spinal cord without any involvement of the primary sites other than the central nervous system. The prevalence of this disease is higher in the elderly population with a median of 65 years as the age of the patient population [2, 3].

High-dose methotrexate (MTX)-based systemic chemotherapy is widely accepted in current practice, and several clinical trials investigating combination regimens of rituximab with cytotoxic chemotherapy have shown promising results [4, 5]. Although no standard treatment has been established, consolidation therapy is necessary to improve outcomes in patients who achieved a complete response after induction treatment. Physicians are moving away from whole-brain radiotherapy (WBRT), a traditional approach for consolidation, due to the risk of neurotoxicity [4, 6].

In the past few years, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) has been developed as an alternative consolidative strategy in PCNSL [4]. Several high-dose chemotherapy regimens were introduced including BCNU, etoposide, cytarabine, and melphalan (BEAM) and thiotepa-containing regimens [7–9]. However, no study directly compared the outcomes of the different high-dose chemotherapy regimens [4].

Asan Medical Center used the combination of busulfan, cyclophosphamide, and etoposide (BuCyE) as the standard high-dose chemotherapy in ASCT therapy until the thiotepa, busulfan, and cyclophosphamide (TBC) regimen was introduced in December 2012, when thiotepa was reimported and approved for usage in ASCT conditioning regimen for treating PCNSL in Korea. The purpose of this study was to compare the outcome and toxicity profile of BuCyE with that of TBC followed by ASCT as consolidation therapy in PCNSL patients with prior response to systemic induction chemotherapy.

Materials and methods

Patients

The PCNSL prospective registry data set, collected from March 1993 to May 2017 at Asan Medical Center, was reviewed retrospectively. Patients who achieved a complete response (CR) or partial response (PR) after induction chemotherapy and who received BuCyE or TBC followed by ASCT as consolidation therapy were included in the study. Patients were stratified into two groups based on the high-dose chemotherapy regimen received during consolidation therapy (TBC vs. BuCyE).

Patients who achieved CR or PR after two initial cycles of chemotherapy and whose age was < 65 years and ECOG performance status was 0–2 were selected for consolidation therapy with ASCT. These patients underwent autologous stem cell mobilization and collection during the fifth or sixth cycle of chemotherapy with daily colony stimulating factor (CSF) administration, as previously described [10].

Induction treatment

All patients received a combination of high-dose MTX- and high-dose cytarabine-based treatment. Fifty-two patients received high-dose MTX and high-dose cytarabine (HDMA) regimen with 3.5 g/m^2 MTX intravenous (IV) infusion for 2 to 3 h on day 1 and leucovorin rescue from day 2. MTX was administered every 2 weeks for 5 cycles. On the fifth and sixth cycles of chemotherapy, 3 g/m^2 cytarabine was administered (IV infusion) for 2 h on days 2 and 3 every 1 month [11]. One patient received methotrexate, vincristine, and procarbazine (MPV) regimen with high-dose cytarabine as previously described. Induction chemotherapy regimen was selected at the treating physician's discrete. None of the patients could receive rituximab during induction chemotherapy due to the non-approval of the drug for treatment of PCNSL by the Korean Ministry of Food and Drug Safety.

Response to chemotherapy was assessed after 2 to 3 cycles of chemotherapy by brain magnetic resonance (MR) according to the criteria of the International Workshop on Evaluation of Primary Central Nervous System Lymphoma [12].

High-dose chemotherapy followed by autologous stem cell transplantation

The BuCyE group received busulfan (3.2 mg/kg IV) on day 7 (7 days before stem cell infusion) to day 5, etoposide (200 mg/m^2 IV) on day 5 to day 4, cyclophosphamide (50 mg/kg IV) on day 3 to day 2, and stem cell infusion on day 0. The TBC group received thiotepa (250 mg/m^2 IV) on day 9 to day 7, busulfan (3.2 mg/kg IV) on day 6 to day 4, cyclophosphamide (60 mg/kg IV) on day 3 to day 2, and stem cell infusion on day 0 (Fig. 1).

CSF was administered daily from day 1 of ASCT until neutrophil counts were > 1000/mm^3 for three consecutive days. Neutrophil engraftment was defined as the first of three consecutive days of absolute neutrophil count $\geq 0.5 \times 10^9$/L, and platelet engraftment was defined as the day that platelet count $\geq 20 \times 10^9$/L with no requirement for platelet transfusion. Patients received ciprofloxacin, acyclovir, and micafungin as prophylaxis from the day after stem cell infusion until neutrophil count $\geq 0.5 \times 10^9$/L for three consecutive days. The treatment responses were evaluated 1 month after ASCT, every 3 months for the first 2 years, and every 6 months for the rest by brain MR imaging. Disease progression or relapse was determined by the previously mentioned criteria [11].

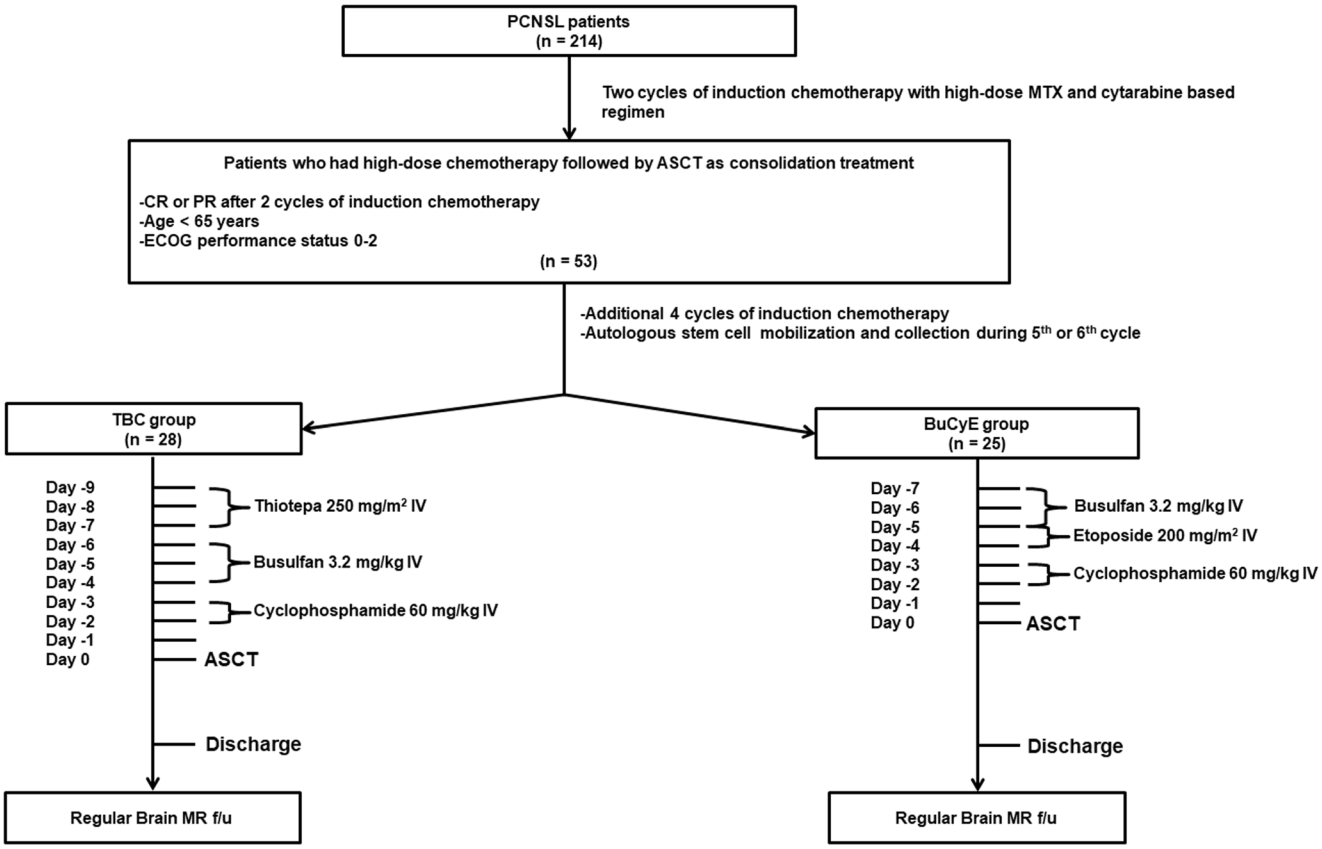

Fig. 1 Study outline

Statistics

Overall survival (OS) was defined as the time from the initiation of the conditioning regimen to death by any cause, and progression-free survival (PFS) as the time from the initiation of the conditioning regimen to treatment failure or death by any cause. Treatment failure is defined as disease progression or relapse after ASCT confirmed by brain MR. Any of the following are regarded as treatment failure: A more than 25% increase in the contrast-enhancing lesion seen on MRI as compared with baseline or best response and the appearance of any new lesions [11]. To adjust for potential follow-up time bias between the two treatment groups, additional survival comparison was performed by censoring the patients receiving BuCyE at 4.4 years (longest follow-up in the TBC group). Survival curves were estimated by Kaplan-Meier methods and compared using log-rank tests. Univariate analyses were performed to identify prognostic factors for PFS and OS using a Cox proportional hazards model. Chi-square tests were conducted to compare variables between the two groups as appropriate. The Mann-Whitney *U* test was conducted to evaluate the differences between two sets of continuous variables including the number of infused $CD34^+$ cells, time to bone marrow engraftment, and hospitalization duration. A two-sided p value < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (IBM Corp, Armonk, NY, USA) 21.0.

Results

Clinical characteristics

A total of 53 patients with a diagnosis of PCNSL who had high-dose chemotherapy followed by ASCT after responses to induction treatments were enrolled. The median age was 53 years and 13 patients (24.5%) were ≥ 60 years of age. The median follow-up duration of the survivors was 4.0 years (range, 0.3–10.3). The median OS of the study population was 8.7 years (95% CI, 4.6–12.9), and the median PFS was 6.5 years (95% CI, 3.0–10.0). Twenty-eight patients (52.8%) were male, 27 patients (50.9%) achieved CR, and 26 patients (49.1%) achieved PR. All the patients had a pathologic diagnosis of diffuse large B cell lymphoma (DLBCL). The 2-year OS and PFS rates of the entire cohort were 78.4% and 65.3%, respectively.

Conditioning regimen was TBC in 28 patients and BuCyE in 25 patients. The comparison of baseline clinical characteristics between the two groups is summarized in Table 1. There

Table 1 Baseline characteristics

	TBC ($N = 28$)	BuCyE ($N = 25$)	p
Age			0.58
< 60	22 (78.6%)	18 (72%)	
≥ 60	6 (11.4%)	7 (18%)	
Sex			0.01
Male	10 (35.7%)	18 (72%)	
Female	18 (64.3%)	7 (18%)	
ECOG performance status at diagnosis			0.37
0–1	24 (85.7%)	19 (76%)	
2	4 (14.3%)	6 (24%)	
Cerebrospinal fluid protein level at diagnosis			0.36
≥ 50 mg/dL	10 (35.7%)	7 (28%)	
< 50 mg/dL	13 (64.3%)	16 (72%)	
Serum lactate dehydrogenase at diagnosis			0.56
> 250 IU/L	8 (28.6%)	9 (36%)	
≤ 250 IU/L	20 (71.4%)	16 (64%)	
Best response to induction chemotherapy			0.01
Complete response	10 (35.7%)	21 (84%)	
Partial response	18 (64.3%)	4 (16%)	

ECOG, Eastern Cooperative Oncology Group

were no statistically significant differences between the two groups except the presence of more male than female patients in the BuCyE group and the presence of more patients who achieved CR before consolidation therapy in the BuCyE group than in the TBC group. Since the TBC regimen was adopted at Asan Medical Center in December 2012, patients in each group underwent ASCT at different periods. Patients who were treated before December 2012 received BuCyE, while TBC was given to patients who had treatment after December 2012. Follow-up time was significantly different between the two groups with a median follow-up duration of 1.9 years (range, 0.3–4.4) of all patients in the TBC group and 4.6 years (range, 0.4–9.9) in the BuCyE group ($p = 0.004$). Four patients in the TBC group who were > 60 years of age received busulfan and cyclophosphamide with a 25% dose reduction.

Survival outcome

Median OS was not reached in the TBC group, while the BuCyE group showed a median OS of 4.9 years (95% CI, 2.0–7.9; $p = 0.02$). The 2-year OS rates were 88.1% and 64% in the TBC and BuCyE groups, respectively. Median PFS was not reached in the TBC group, while the BuCyE group had a median PFS of 1.1 years (95% CI, 0.0–2.7; $p < 0.01$). The 2 year PFS rates were 84.7% and 40% in the TBC and BuCyE groups, respectively. The estimated survival curves are shown in Fig. 2. Survival differences could be explained by potential follow-up time bias between the two groups. We therefore tried to adjust this likely bias by performing additional survival comparison truncating patients who had follow-up duration longer than 4.4 years at 4.4-year time point, as longest follow-up duration in TBC group was 4.4 years. Survival differences between the two groups were also found in terms of OS and PFS with truncation of follow-up period at 4.4 years from the initiation of conditioning regimen (Supplementary Fig. 1). Univariate analysis of potential prognostic factors, including age, sex, ECOG performance status, and response to induction chemotherapy, did not show statistically significant survival differences (Supplementary Table 1).

Toxicity profiles

The toxicities that occurred during high-dose chemotherapy and ASCT in each treatment group are described in Table 2 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). Gastrointestinal toxicity of any grade was significantly higher in the TBC group than in the BuCyE group. Grade 3 or 4 toxicities including mucositis, diarrhea, and nausea were significantly more frequent in the TBC group than in the BuCyE group. There was no case of treatment-related mortality. Hemorrhagic complication was reported in one patient of the TBC group, grade 2 hematochezia due to typhilitis.

All patients in the TBC group and 16 patients in the BuCyE group received prophylactic antimicrobial agents

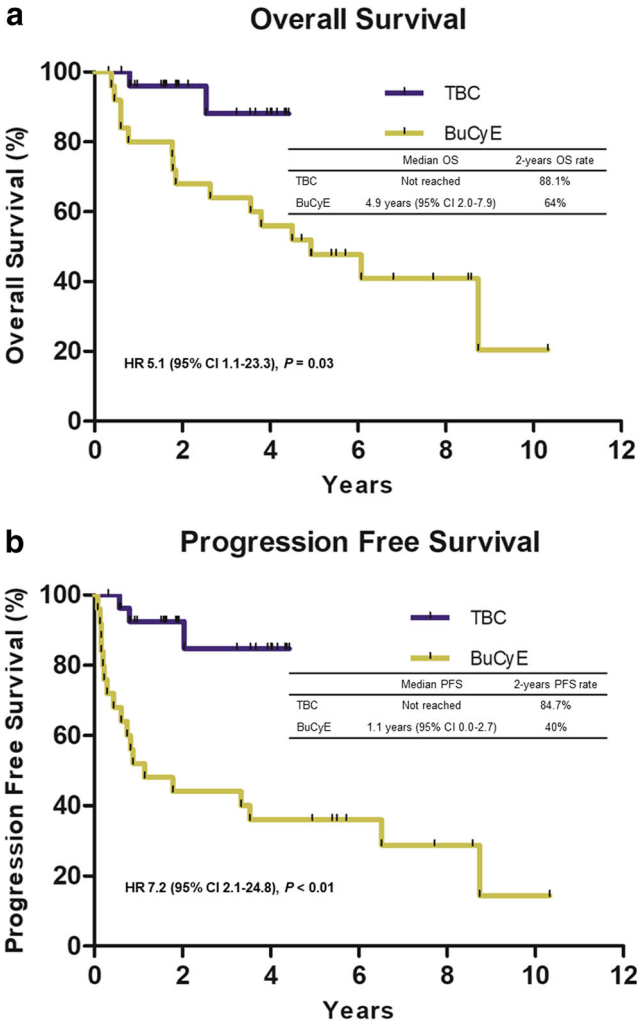

Fig. 2 Overall survival and progression-free survival based on high-dose chemotherapy regimen. **a** Overall survival. **b** Progression-free survival

as previously described. Twenty-six patients in the TBC group had febrile neutropenia, and three patients had grade 4 febrile neutropenia requiring intensive care. Twenty patients in the BuCyE group had febrile neutropenia (Table 3).

Hospitalization duration, days to bone marrow engraftment, and infused stem cell dose are summarized in Table 4. The median numbers of infused $CD34^+$ cells were similar between the two groups. Neutrophil engraftment was significantly faster in the TBC group compared with the BuCyE group, and platelet engraftment was similar between the two treatment groups. The median duration of hospitalization was also similar between the two groups.

Discussion

For PCNSL patients with response to induction systemic chemotherapy, consolidation therapy with high-dose chemotherapy and ASCT is a reasonable treatment strategy [13]. Several conditioning regimens have previously been investigated with only a few evidences supporting the superiority of a regimen over others, although a comprehensive review suggested better efficacy outcomes of thiotepa-based regimens compared to others [14]. In this present study, we compared survival outcomes and toxicity profiles between the TBC and BuCyE regimen as consolidative high-dose chemotherapy followed by ASCT for PCNSL patients responding to high-dose MTX-based induction chemotherapy.

In our study, the TBC group showed better survival outcomes compared to the BuCyE group in terms of OS and PFS. The incidence of adverse events associated with mucosal damage was higher in the TBC group; however, hospitalization duration and days to engraftment were comparable between the two groups. The survival benefit of the TBC group may be greater considering that more patients with CR as best response to induction chemotherapy is in the BuCyE group compared to the TBC group. Also, 4 of 6 patients older than 60 years in the TBC group received reduced dose of busulfan and cyclophosphamide.

There are several studies of the TBC regimen followed by ASCT in PCNSL patients after induction chemotherapy. A

Table 2 Toxicities of conditioning regimens

	Any			Grade 3–4		
	TBC ($N = 28$)	BuCyE ($N = 25$)	p	TBC ($N = 28$)	BuCyE ($N = 25$)	p
Mucositis	27 (96.4%)	20 (80%)	< 0.01	16 (57.1%)	0	< 0.01
Diarrhea	26 (92.9%)	13 (52%)	< 0.01	14 (50%)	2 (8%)	< 0.01
Nausea	24 (85.7%)	11 (44%)	< 0.01	6 (21.4%)	0	0.01
Vomiting	20 (71.4%)	5 (20%)	< 0.01			
AST, ALT	18 (64.3%)	13 (52%)	0.37	1 (3.6%)	0	1
Bilirubin	8 (28.6%)	3 (12%)	0.18	3 (10.7%)	0	0.24
Azotemia	5 (17.9%)	0	0.05			

AST, aspartate transaminase; *ALT*, alanine transaminase

Table 3 Adverse event related to infection and antimicrobial usage

	TBC ($N = 28$)	BuCyE ($N = 25$)
Usage of prophylactic antimicrobial agent	28 (100%)	16 (64%)
Febrile neutropenia, grade 3	23 (82.1%)	20 (80%)
Febrile neutropenia, grade 4	3 (10.7%)	0
Confirmed bacterial infection	5 (17.9%)	3 (12%)
Empirical antibiotics for febrile neutropenia	$N = 26$	$N = 20$
Cefepime ± vancomycin	26 (100%)	5 (25%)
Piperacillin-tazobactam ± vancomycin		7 (35%)
Ceftazidime + amikacin ± vancomycin		8 (40%)

single-center retrospective study of 46 PCNSL patients who achieved CR after induction chemotherapy resulted in 2-year OS of 95% and 2-year PFS of 92%, with severe mucositis occurring in 35% of the patients [15]. The superior survival outcomes of this study compared to 2-year OS and PFS of 88.1% and 84.7% in the TBC group of our study might arise from the lack of rituximab usage during induction treatment in our center. Thus, our study results strengthen the necessity of combining rituximab in induction chemotherapy for PCNSL. Another phase 2 single-center study of 32 PCNSL patients who achieved CR or PR after 5–7 cycles of rituximab, MTX, procarbazine, and vincristine (R-MPV) induction chemotherapy resulted in 2-year OS and PFS of 81% and 79% [16]. Despite the usage of rituximab-containing induction chemotherapy, survival outcomes were comparable to our results. The fact that a proportion of patients with age 60 years or older and poor performance was higher than our TBC group might explain the results. This could implicate that the application of the TBC regimen in patients with poor performance or old age should be performed cautiously.

Thiotepa and carmustine combination regimen is also well-studied and is currently an available option as conditioning regimen for ASCT in PCNSL. In a phase 2 international randomized trial comparing WBRT with ASCT as consolidation treatment in PCNSL, 59 patients were randomized to ASCT group after response to induction chemotherapy [17]. Patients received 400 mg/m^2 of carmustine on day 1, thiotepa 5 mg/kg every 12 h on days 2 and 3, and received stem cell infusion on day 7. Survival outcome was inferior compared with the TBC group but higher than the BuCyE group in our study with a 2-year PFS of 69%. A multicenter phase 2 trial with 73 patients with PCNSL was conducted in Germany, and rituximab in combination with thiotepa and carmustine was applied as high-dose chemotherapy followed by ASCT [18]. With a median follow-up duration of 57.4 months, 3-year OS rate was 81% and PFS rate was 67%. Based on these results compared to survival outcomes of the TBC group and the BuCyE group in our study, usage of thiotepa in high-dose chemotherapy consolidation for PCNSL may have importance for better outcomes.

High-dose chemotherapy conditioning regimens without thiotepa or busulfan showed inferior efficacy compared to thiotepa-containing regimens. The efficacy of the BEAM regimen was evaluated as conditioning regimen for ASCT in a prospective study of 14 patients with response to HDMA induction chemotherapy and resulted in a 2-year OS of 60% with a median event-free survival (EFS) of 9 months [11].

Several factors might explain the superior survival outcome of TBC compared with BuCyE. Thiotepa and busulfan show excellent CNS bioavailability, and the combination of these two drugs contributes to the elimination of remnant tumor cells in the CNS as a result of their ability to cross the blood-brain barrier [19, 20]. Also, both drugs are known to have sharp dose-response curves and could achieve greater efficacy than other drugs when used in high-dose chemotherapy regimen [21]. Indeed, a combination of these two suitable drugs may show better efficacy outcome than a single.

This study has several limitations. First, patients were enrolled in different decades. Therefore, there is a high probability of patients in each group receiving different management in terms of supportive care, for example, empirical antibiotics usage in febrile neutropenia as previously described or management of relapsed and refractory PCNSL. Also, follow-

Table 4 Days to engraftment and duration of hospitalization

	TBC ($N = 28$) median (range)	BuCyE ($N = 25$) median (range)	p
Number of infused CD34$^+$ cells ($\times 10^6$ cells/kg)	35.3 (3.7–76.0)	13.1 (7.7–172.7)	0.78
Time to neutrophils ≥ 500/mm^3 (days)	7 (6–9)	9 (7–13)	< 0.01
Time to platelets ≥ 20,000/mm^3 (days)	8 (5–15)	8 (6–12)	0.70
Hospitalization duration (days)	16 (10–42)	18 (14–36)	0.35

up time was significantly different between the two groups ($p = 0.004$), potentially introducing a time bias. We performed additional survival comparison to adjust follow-up time bias by truncating follow-up period at 4.4 years, and the results were consistent. Second, our study is a retrospective analysis performed in a single-center population with a small-sized cohort. Third, the patients did not receive rituximab-containing induction chemotherapy which is now widely accepted as it was not approved for an indication in Korea. Also, comparison of neurotoxicity outcomes or quality of life was not performed.

A key strength of the present study is that all patients received high-dose MTX- and high-dose cytarabine-based induction chemotherapy. The stem cell mobilization and collection protocol were also the same in both groups, enhancing the reliability of the comparison of survival between the two groups. In conclusion, TBC showed better survival outcomes than BuCyE as high-dose chemotherapy followed by ASCT in the context of consolidation therapy for PCNSL patients who achieved CR or PR after 6 cycles of HDMA.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required (IRB 2018-1275).

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

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