R-MPV Followed by High-dose Chemotherapy With Thiotepa-based and Autologous Stem Cell Transplantation for Newly Diagnosed Primary Central Nervous System Lymphoma: A Single-center Experience

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Abstract

Background

High-dose chemotherapy followed by autologous stem-cell transplantation (HDC–ASCT) as a consolidation treatment is a promising approach in eligible patients with newly diagnosed primary central nervous system lymphoma (PCNSL). This study sought to assess the safety and efficacy of initial methotrexate-based chemotherapy followed by consolidation HDC-ASCT with a thiotepa-based conditioning regimen in patients with newly diagnosed PCNSL.

Methods

In this retrospective analysis, 22 patients with newly diagnosed PCNSL received chemotherapy with rituximab, methotrexate, procarbazine, and vincristine (R-MPV). Those who showed a complete or partial response subsequently received consolidation HDC-ASCT with a thiotepa-based conditioning regimen and no radiotherapy.

Results

Characteristics of the PCNSL patients included a median age of 57 years (range: 49–67 years), Eastern Cooperative Oncology Group performance status of grade 2 or more in 9.1%, elevated lactate dehydrogenase level in 26.3%, and involvement of multiple lesions in 72.1%. About 82% of patients received six cycles of induction chemotherapy, which was well-tolerated with excellent disease control. The rate of confirmed/or unconfirmed complete response increased from 45.5% in the interim to 81.8% before HDC-ASCT. With a median follow-up of 19.6 months (range: 7.5–56.5 months), the 2-year progression-free survival and overall survival estimates were 84% and 88%, respectively. There were no treatment-related deaths. Grade 3 toxicity was recorded in 90.9% after HDC-ASCT, and the most common grade 3 adverse event was febrile neutropenia without sepsis.

Conclusions

The discussed treatment approach appears feasible in patients with newly diagnosed PCNSL, yielding encouraging results.

Background

Primary central nervous system lymphoma (PCNSL) is an aggressive form of extranodal non-Hodgkin lymphoma that involves the brain, meninges, eyes, and/or spinal cord without systemic involvement[1]. PCNSL accounts for 3% to 4% of all primary brain tumors and 4% to 6% of extranodal lymphomas[2].

First-line induction chemotherapy regimens incorporating high-dose methotrexate (HD-MTX) are considered the standard of care for newly diagnosed PCNSL[3]. HD-MTX is commonly used in combination with other drugs such as vincristine, procarbazine, cytarabine, rituximab, and temozolomide,

resulting in high rates of initial response of 69% to 95%[4-6]. While PCNSL is sensitive to chemotherapy, more than half of patients who show a complete response (CR) will experience relapse within five years[7]. Consolidative whole-brain radiotherapy (WBRT) has been the most commonly adopted treatment strategy to prolong remission after induction therapy[8]. However, major concerns regarding neurotoxicity, which can have a tremendous impact on quality of life in long-term survivors, have prompted the search for alternative consolidative strategies[9, 10].

Prior retrospective and phase II trials have suggested the feasibility and efficacy of high-dose chemotherapy followed by autologous stem-cell transplantation (HDC-ASCT) as a consolidation treatment for patients with PCNSL[11-15]. Most trials addressing HDC-ASCT have included only a small number of patients with a short period of follow-up and have demonstrated differences in clinical features and conditioning regimens. In addition, a proportion of patients in these studies also received WBRT given either as adjuvant treatment post-ASCT to all patients or to patients who did not achieve a CR to induction. Thus, interpreting the results of HDC-ASCT with respect to efficacy and feasibility using these prior data is difficult.

A recent phase II trial of a combination of rituximab, methotrexate, procarbazine, and vincristine (R-MPV) followed by HDC-ASCT with a thiotepa, busulfan, and cyclophosphamide (TBC) conditioning regimen achieved excellent disease control, a 2-year progression-free survival (PFS) rate of 79%, and acceptable toxicity profiles with minimal neurotoxicity in patients with newly diagnosed PCNSL[16]. This retrospective study sought to report further on the use of R-MPV followed by thiotepa-based HDC-ASCT as consolidation in patients with newly diagnosed PCNSL.

Methods

Patients

Between January 2015 and December 2019, a total of 22 patients with newly diagnosed PCNSL who received thiotepa-based HDC-ASCT as consolidation therapy at Seoul National University Bundang Hospital were retrospectively reviewed. All had a biopsy-proven diagnosis of PCNSL with diffuse large B-cell lymphoma histology except one patient at risk of postoperative neurologic deficit. Baseline patient characteristics collected for analysis were age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), lactate dehydrogenase (LDH), cerebrospinal fluid (CSF) protein concentration, and CSF cytology. Assessment of clinical prognostic factors was performed based on the International Extranodal Lymphoma Study Group (IELSG) score[17].

Treatment and Response Evaluation

All patients received induction chemotherapy with rituximab, methotrexate, procarbazine, and vincristine (R-MPV) given as follows: day 1, rituximab 375 mg/m^2; day 2, methotrexate 3.0 g/m^2 (over three hours), vincristine 1.4 mg/m^2; and days 1 through 7, procarbazine 100 mg/m^2/d (odd cycles only). Hydration and leucovorin rescue were conducted according to institutional guidelines. Patients with CSF evidence

of malignancy received 15 mg of intrathecal methotrexate between cycles. Patients with CR, unconfirmed CR (uCR), or partial response (PR) proceeded directly to HDC-ASCT.

Separately, patients received busulfan/thiotepa (Bu/TT) or TBC as a conditioning chemotherapy regimen. The Bu/TT group received busulfan (3.2 mg/kg intravenously) from day 8 (eight days before stem cell infusion) to day 5, thiotepa (5 mg/kg intravenously) from day 4 to day 3, and stem cell infusion on day 0. The TBC group received thiotepa (250 mg/m^2 intravenously) from day 9 to day 7, busulfan (3.2 mg/kg intravenously) from day 6 to day 4, cyclophosphamide (60 mg/kg intravenously) from day 3 to day 2, and stem cell infusion on day 0. G-CSF was administered daily from day 1 of ASCT until the neutrophil count was < 3,000 cells/mm^3. Neutrophil and/or platelet engraftment was defined as an absolute neutrophil count >0.5×10^9/L in the first three consecutive days and a platelet count >20×10^9/L without transfusion support, respectively. A decreased intensity of the TBC or Bu/TT regimen was used for patients older than 60 years or less fit patients based on the clinical judgment of the physician (Supplementary Table 1).

Response to treatment was assessed with contrast-enhanced brain magnetic resonance imaging (MRI), which was performed after two or three cycles of chemotherapy and before HDT-ASCT. Treatment response was defined based on changes in tumor size of enhanced lesions on T1-weighted MRI and following the National Cancer Institute standardized response criteria[18]. Severity of adverse events was graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

The primary outcome measures were response rate, PFS, and overall survival (OS) after diagnosis. OS was defined as the time from initiation of the induction regimen to death by any cause, while PFS was defined as the time from initiation of the induction regimen to treatment failure or death by any cause. Survival curves were estimated by the Kaplan–Meier method and compared using the log-rank test. Univariate analyses were performed to identify prognostic factors for PFS and OS using a Cox proportional-hazards model. Chi-square test was conducted to compare variables between the two groups as appropriate. All tests were two-tailed, and differences were considered significant at $p < 0.05$. All statistical analyses were performed using Statistical Package for the Social Sciences version 18.0 (SPSS, Chicago, IL, USA).

Results

Patient Characteristics

The median age of the study group was 57 years (range: 59–67 years), and 31.8% of patients were older than 60 years. Also, 59.1% of patients were male. At baseline, 9.1% of our cohort had an ECOG PS of grade 2 or above, 26.3% had an elevated LDH level, and 95.5% showed an elevated CSF protein concentration. Among the 19 patients for whom complete IELSG PCNSL prognostic parameters were

available, 17 (89.5%) presented an intermediate to high level of risk. Two patients (9.1%) had positive CSF cytology, 13.6% had intraocular lymphoma, and 72.7% had multiple brain lesions. No patient had evidence of systemic lymphoma at the time of study enrollment.

Induction Chemotherapy

A majority of patients (18 patients; 81.8%) received six cycles, three patients (13.6%) received five cycles, and one patient (4.5%) received eight cycles of induction chemotherapy. The details of the response to treatment are outlined in Table 2. During interim analysis after induction chemotherapy, 10 patients (45.5%) achieved a CR/CRu and 12 patients (54.5%) achieved a PR. At the end of induction chemotherapy, eight of the patients who had previously achieved a PR ultimately achieved a CR/CRu. Therefore, following completion of induction chemotherapy, 18 patients (81.8%) achieved a CR/CRu and four patients (18.2%) achieved a PR.

Induction chemotherapy was well-tolerated with no treatment-related deaths or treatment discontinuations because of toxicity. Grades 3 and 4 toxicities were noted in 50.5% and 4.5% of patients, respectively. Nine patients (40.9%) developed grade 3 neutropenia, but no cases of febrile neutropenia occurred. Four patients (18.2%) showed grade 3 hepatic impairment but recovered to baseline values with daily liver function monitoring and hydration. One patient demonstrated grade 4 hepatic impairment after cycle 1; this individual omitted rituximab during subsequent chemotherapy cycles because rituximab was the only drug that the patient had received immediately preceding liver function deterioration.

High-dose Chemotherapy and Autologous Stem Cell Transplant

Characteristics of the HDC-ASCT treatment are summarized in Table 3. All patients underwent therapy with TBC (n = 12; 54.5%) or Bu/TT (n = 10; 45.5%) as a conditioning regimen followed by ASCT. The median number of infused $CD34^+$ cells was 6.7×10^6 cells/kg (range: $4.1–21.1 \times 10^6$ cells/kg). The median number of days to neutrophil engraftment and platelet recovery were nine days (range: 7–11 days) and 10 days (range: 7–12 days), respectively. The median length of the transplantation-related hospitalization stay was 21 days (range: 18–44 days).

There was no instance of treatment-related mortality (TRM). Grade 3 toxicities were observed in 90.9% of patients, and no grade 4 toxicities were recorded. The most common grade 3 adverse events were febrile neutropenia (86.4%), diarrhea (27.3%), mucositis (22.7%), colitis (18.2%), and nausea (13.6%). Of the 19 patients with febrile neutropenia, two had bacteremia, but they recovered with appropriate antibiotic treatment without sepsis.

PFS and OS

The PFS and OS curves are shown in Figure 1. After a median follow-up period of 19.6 months (range: 7.5–56.5 months), 19 patients (86.4%) were alive and 17 patients (77.3%) were without disease progression. The median PFS and OS were 38.7 months (95% confidence interval: 23.6–49.6) and 43.5

months (95% confidence interval: 31.3–55.7), respectively. The 2-year PFS and OS estimates were 84% and 88%, respectively.

Four patients (18.2%) showed relapse in the CNS and received second-line treatment. One patient who experienced a relapse approximately 20 months after transplantation is alive after having received several salvage therapies, while another patient who had a relapse approximately eight months after transplantation died from progressive lymphoma refractory to salvage therapy. One patient is currently undergoing WBRT treatment and another other died of pneumonia after salvage WBRT. One patient died of aspiration pneumonia with no evidence of disease recurrence.

Discussion

In this retrospective study, patients with newly diagnosed PCNSL were treated with R-MPV induction chemotherapy, followed by consolidation HDC-ASCT with a thiotepa-based conditioning regimen in patients who showed a response and no further treatment until disease progression.

Regarding the adopted treatment strategy, there are two major points that should be discussed. First is the efficacy of the induction regimen with R-MPV therapy before ASCT. On the basis of retrospective comparisons with historical controls, addition of rituximab to HD-MTX–based chemotherapy improves the chance of complete response and overall survival in patients with newly diagnosed PCNSL[19-21]. Recently, results from the first randomization of the IELSG 32 trial indicated that addition of rituximab and thiotepa to conventional methotrexate–cytarabine combination therapy (known as the MATRix regimen) was associated with an overall response rate (ORR) of 87% and a 2-year PFS rate of 62% without higher rates of severe complications[22]. According to recent studies, the R-MPV regimen has shown excellent efficacy with CR rates of 69% to 79% and ORR rates of 95% to 96% at the end of induction chemotherapy[6, 16]. The present study has limitations inherent to any retrospective analysis, and no data from the patients in whom HDC-ASCT was intended but not actually used. Nevertheless, a significant increase in CR/CRu was observed during induction chemotherapy, increasing from 45.4% at the time of interim analysis to 81.8% before HDC-ASCT.

The second discussion point of note is the efficacy and tolerability of the conditioning regimen for ASCT. Although no formal comparison of conditioning regimens has been conducted to date, historical results gathered after using the BEAM regimen [carmustine (BCUY), etoposide, cytarabine, and melphalan] were disappointing, with a modest treatment response rate and a 2-year OS rate of 60%[11]. According to the meta-analysis by Alnahhas et al., BCNU/TT carried the lowest risk of TRM and an equivalent response rate to that of TBC, while TBC achieved a lower relapse rate and numerically superior OS and PFS rates[23]. A recent investigation by Omuro et al. found that the 2-year PFS and OS rates in their study population were both 81% with a median follow-up period of 45 months[16]. TBC is an effective conditioning regimen, but its toxicities remain a major concern requiring further focus. Septic complications, mostly bacterial infections occur in one-third of treated patients, with grade 3 or greater febrile neutropenia found in 42% of patients and a TRM of up to 19%[24-26]. At our institution, young and

fit for intensive therapy have been used as criteria to evaluate readiness for TBC as conditioning regimen as suggested by Omuro et al.[16], whereas decreased-intensity TBC and Bu/TT regimens have been used in those older than 60 years or who are less fit. The current study reported a high response rate with a significant improvement in CR/CRu, from 81.8% before HDC-ASCT to 100% after HDC-ASCT. In addition, the 2-year PFS and OS rates were favorable at 84% and 88%, respectively. In this study, the median OS and PFS rates were lower than those in the previous study by Omura et al[16] because one patient died of pneumonia in this study, unrelated to their disease. No serious complications during treatment or TRM were observed, which is notable despite the study's major limitations such as its small patient number and the relatively short follow-up period.

Despite the significant improvements in management of PCNSL, nearly half of responders will relapse, which occurs within two years after initial diagnosis[27, 28]. After a median follow-up period of 19.6 months, about 18% of patients showed relapse. Although only limited interpretation can be performed due to the small number of patients and short follow-up period, the patients who relapsed within one year after ASCT had poorer survival outcomes. Treatment of relapsed and refractory (R/R) PCNSL remains a major area of unmet clinical need. The prognosis of R/R PCNSL is very poor, with a median OS of three to five months[29]. Further clinical trial data are required to guide therapeutic management in this group of patients.

The present study has several limitations. Given the single-center, retrospective nature of this investigation, undefined bias concerning the clinical outcomes might exist. Interpretation of the results should be performed with caution due to the small sample size and relatively short follow-up duration, most patients (68%) included in this study were diagnosed from 2018 onward. Our study could not verify the IELSG score for prognostication of survival. Increased CSF protein level was associated with a poor prognosis[17, 30, 31]. However, adopting CSF parameters as survival predictors is problematic especially given the difficulty related to choosing the cutoff level to define unfavorable features. In the IELSG scoring system, the cutoff for a normal CSF protein concentration was 45 mg/dL in patients 60 years or younger but 60 mg/dL in patients older than 60 years[17]. When applying these cutoff values, about 95% of patients showed elevated CSF protein concentrations, so CSF protein concentration was thought not to be suitable for discrimination as a prognosis factor for discrimination in the current study. Different laboratory methodologies account for significant discrepancies across institutions and published reference intervals[32]. In other words, the CSF protein concentration cutoff as a predictor of prognosis cannot be applied uniformly. Further studies for a well-established prognostic scoring system with a better knowledge of PCNSL, especially with inclusion of histopathologic and molecular variables, are needed. Finally, formal neurocognitive and quality-of-life assessments were not performed.

Conclusions

In conclusion, R-MPV followed by thiotepa-based HDC-ASCT as consolidation resulted in good response rates and a favorable toxicity profile among patients with newly diagnosed PCNSL.

Abbreviations

PCNSL: Primary central nervous system lymphoma; HD-MTX; High-dose methotrexate; CR: Complete response; WBRT: whole-brain radiotherapy; HDC-ASCT: High-dose chemotherapy followed by autologous stem-cell transplantation; R-MPV: Rituximab, methotrexate, procarbazine, and vincristine; TBC: Thiotepa, busulfan, and cyclophosphamide; PFS: Progression-free survival; ECOG: Eastern Cooperative Oncology Group performance status; LDH: Lactate dehydrogenase; CSF: Cerebrospinal fluid; IELSG: International Extranodal Lymphoma Study Group; R-MPV: Rituximab, methotrexate, procarbazine, and vincristine; uCR: Unconfirmed CR; PR: Partial response; Bu/TT: Busulfan/thiotepa; MRI: Magnetic resonance imaging; OS: Overall survival; TRM: Treatment-related mortality; ORR: Overall response rate; R/R: Relapsed and refractory

Declarations

Acknowledgements

Not applicable.

Authors' contributions

JYL and JOL conceived and designed the study protocol. JYL, KJS, JWK, SHK, JWK, YJK, KWL, JHK, SMB, JOL, and JSL provided of study materials. JYL, JHP, and JOL participated in data collection and analysis. All authors contributed to subsequent drafts and commented and revised on the final draft paper. All authors contributed to the final approval of the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

The study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Bundang Hospital. The need for patient consent was waived by the IRB due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Tables

Table 1. Patient characteristics (n = 22)

Characteristics	No.	%
Age, median years (range)	57 (49-67)	
Age > 60 years	7	31.8
Male sex	13	59.1
ECOG PS ≥ 2	2	9.1
Elevated LDH*	5	26.3
Elevated CSF protein†	21	95.5
Deep brain lesions	16	72.7
IELSG risk group*		
Low	2	10.5
Intermediate	14	73.7
High	3	15.8
Positive CSF cytology	2	9.1
Ocular involvement		
Positive or suspicious	3	13.6
Negative	16	72.7
Unknown	3	13.6
Multiple lesions	16	72.7

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; CSF, cerebrospinal fluid; IELSG, International Extranodal Lymphoma Study Group

*Data regarding serum LDH and IELGS risk group was available in 19 patients.

†The cutoff for normal CSF protein concentration was 45 mg/dL in patients ≤ 60 years old and 60 mg/dL in patients more than 60 years old.

Table 2. Treatment response

Response	Induction_interim		Pre-HDC-ASCT		Post-HDC-ASCT		Follow-up	
	N	%	N	%	N	%	N	%
CR	3	13.6	8	36.4	18	81.8	16	72.7
CRu	7	31.8	10	45.4	4	18.2	2	9.1
PR	12	54.5	4	18.2	0	0	0	0
PD	0	0	0	0	0	0	4	18.2

Abbreviations: CR, complete response; CRu, CR unconfirmed; PR, partial response; PD, progressive disease; HDC-ASCT, high-dose chemotherapy and autologous stem cell transplant.

Table 3. HDC-ASCT characteristics

	No.	%
Conditioning regimen		
TBC	12	54.5
Bu/TT	10	45.5
Number of infused $CD34^+$ cells (× 10 cells/kg), median (range)	6.7 (4.1-21.1)	
Neutrophil engraftment, median days (range)	9 (7-11)	
Platelet engraftment, median days (range)	10 (7-12)	
Transplantation hospitalization, median days (range)	21 (18-44)	

Abbreviations: TBC, thiotepa, busulfan and cyclophosphamide; Bu/TT, busulfan/thiotepa

Figures

Figure 1. Kaplan-Meier curves for OS and PFS

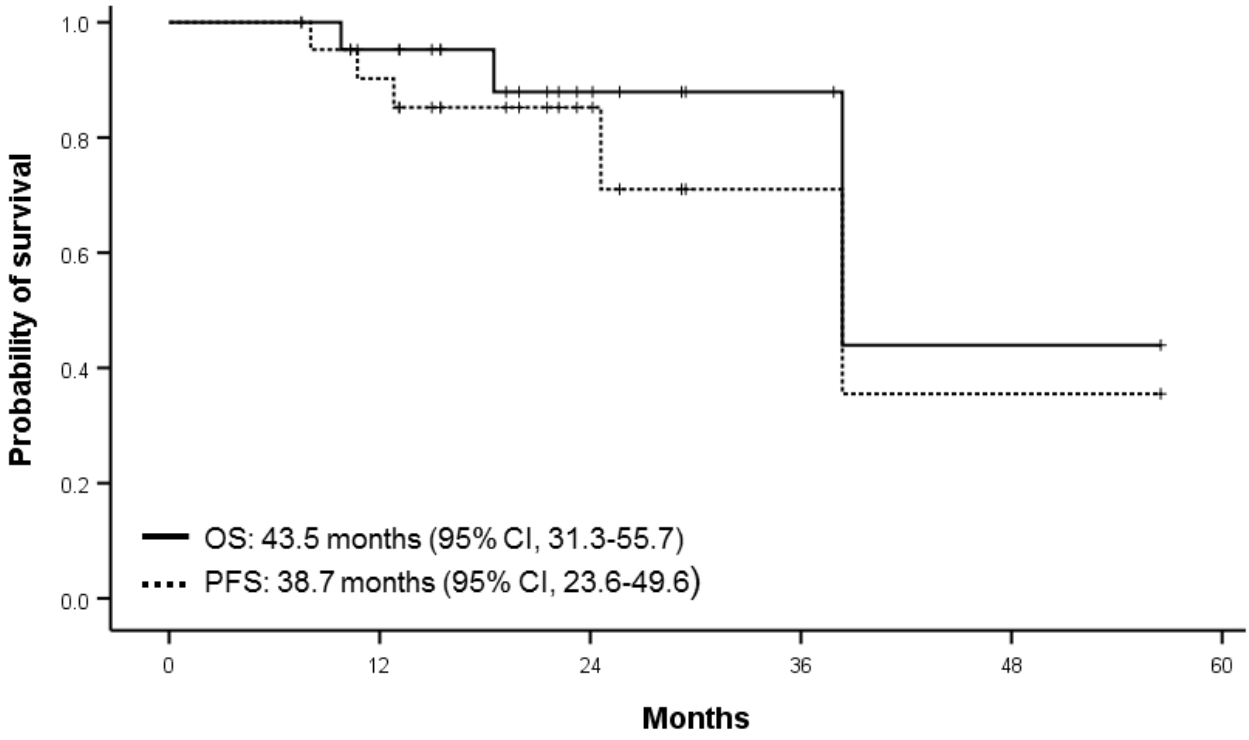

Figure 1

Kaplan-Meier curves for OS and PFS

Supplementary Files

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- SupplementaryTable1.docx