Comparison of the outcomes of patients with primary central nervous system lymphoma between the neurosurgery and hematology/oncology departments based on the relative dose intensity of methotrexate

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Abstract. Primary central nervous system lymphoma (PCNSL) is an extranodal type of lymphoma, which is treated with methotrexate (MTX)-based induction therapy. Although PCNSL is a hematological malignancy, patients with PCNSL may be treated at neurosurgery or hematology/oncology departments; however, the outcomes of PCNSL treatment have not been compared between these two departments. The present study compared the outcomes of 26 patients with newly diagnosed PCNSL that were treated at the Department of Neurological Surgery or Department of Hematology/Oncology (Wakayama Medical University Hospital, Wakayama, Japan) between January 2011 and December 2021. The relative dose intensity (RDI) and relative treatment intensity of MTX were assessed as indicators of the intensity of chemotherapy. The median RDI of MTX was 67 and 93% in the neurosurgery and hematology/oncology groups, respectively (P<0.001). The proportion of patients that achieved a complete response after high-dose MTX-based therapy was significantly higher in the hematology/oncology group than in the neurosurgery group (P=0.038). The estimated 2-year overall survival was 72 and 100% in the neurosurgery and hematology/oncology groups, respectively (P=0.046). As with the difference in the outcomes observed between pediatrics and hematology departments for adolescents with acute lymphoblastic leukemia, the outcomes of patients with PCNSL may differ between neurosurgery and hematology/oncology departments.

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive form of extranodal lymphoma (1). It is classified as a type of non-Hodgkin's lymphoma. Although it is a hematological malignancy, patients that are primarily diagnosed with PCNSL usually present to the neurosurgery department first with intracranial lesions. For a definitive diagnosis, a tissue sample from a brain biopsy needs to be obtained by a neurosurgeon. Due to community referral patterns, patients with PCNSL may be treated at either a neurosurgical department or hematology/oncology department.

High-dose methotrexate (MTX)-based chemotherapy is generally accepted as the standard induction treatment for PCNSL (1). However, the optimal induction regimen, including the optimal combination therapy to add to high-dose MTX, remains uncertain. In addition, no consolidation therapy for use after MTX-based chemotherapy has been established. Recently, intensified chemotherapy, including high-dose chemotherapy with autologous stem cell transplantation (ASCT), has tended to be considered for consolidation therapy in such cases. However, the treatments that can be provided depend on the availability of certain facilities and equipment. For example, ASCT requires specialist equipment for harvesting and preserving hematopoietic stem cells and medical staff capable of performing transplantation procedures. Therefore, treatment methods may vary depending on the department providing the treatment, e.g., neurosurgery and hematology departments may differ in the treatments they can provide for PCNSL. Such differences in the available treatment options among departments may result in different outcomes, just as treatment outcomes for acute lymphoblastic leukemia (ALL) in adolescents and young adults (AYA) differ between pediatric and hematology departments (2). However, the outcomes of PCNSL treatment have not been compared between neurosurgery and hematology/oncology departments.

In chemotherapy for hematological malignancies, it is important to maintain an appropriate therapeutic intensity to achieve better outcomes. Several studies have demonstrated

that maintaining an appropriate relative dose intensity (RDI) during R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy improved survival in newly diagnosed diffuse large B-cell lymphoma (DLBCL) patients (3,4). Recently, the RDI of MTX was reported to have an important prognostic impact in patients with PCNSL (5). However, the difference in the RDI of MTX between treating departments has not been assessed.

Different treatments may be selected by different departments, depending on the expertise of the medical staff, which may lead to differences in treatment outcomes among treating departments. At our hospital, PCNSL patients were treated by the neurosurgery or hematology/oncology department, depending on the year in which they were diagnosed. In this study, we compared the outcomes of PCNSL patients treated at our neurosurgery and hematology/oncology departments based on the RDI of MTX.

Materials and methods

Patients. This was a single-center retrospective study, conducted at Wakayama Medical University Hospital. Consecutive patients with newly diagnosed PCNSL who received high-dose MTX-based therapy between January 2011 and December 2021 were selected via a review of electronic medical records. Patients who received radiotherapy alone or palliative chemotherapy were excluded from this analysis. The selected patients had untreated histologically-proven DLBCL. A PCNSL patient with natural killer/T-cell lymphoma histology was excluded. Patients with PCNSL that were diagnosed between January 2011 and March 2018 were treated at the neurosurgery department (Fig. S1). These patients visited the neurosurgery department for a mass lesion in the brain, underwent a brain biopsy to obtain a definitive diagnosis, and continued to be treated at the neurosurgery department. When patients required multi-drug combination chemotherapy after relapse, they were transferred to and treated at the hematology/oncology department. On the other hand, patients that were diagnosed with PCNSL between April 2018 and December 2021 were treated at the hematology/oncology department from the initial treatment onwards. These patients were referred to the hematology/oncology department once a definitive diagnosis had been made by the neurosurgery department. To assess the impact of the treating department on survival, the patients were classified into those treated at the neurosurgery department and those treated at the hematology/oncology department.

All patients underwent positron emission tomography-computed tomography (PET-CT) or CT (i.e., patients who could not undergo PET-CT) for staging in addition to brain gadolinium-enhanced magnetic resonance imaging (MRI) before the initial treatment. Prognostic factors were evaluated using the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic model and the International Extranodal Lymphoma Study Group (IELSG) model (6,7).

Treatments. Induction therapy was performed with three different regimens: high-dose MTX; rituximab and MTX (R-MTX); and rituximab, MTX, procarbazine, and vincristine (R-MPV). The high-dose MTX treatment regimen consisted of MTX (3.5 mg/m^2) and 15 mg leucovorin (15 mg) every 4 h, starting 24 h after the administration of MTX. In the R-MTX regimen, the high-dose MTX regimen was administered, but rituximab (375 mg/m^2) was added the day before the MTX infusion. In some patients, the first dose of rituximab was administered after MTX. The R-MPV regimen was modified from the original regimen reported by the MSKCC (8). The modified regimen consisted of rituximab (375 mg/m^2) on day 1, vincristine (1.4 mg/m^2, capped at 2 mg/body) on day 2, and procarbazine (100 mg/m^2) orally on days 2 to 8 in addition to the high-dose MTX regimen, starting on day 2. Procarbazine was only administered during odd cycles. The dose of MTX was reduced at the attending doctor's discretion, based on the patient's performance status and the presence/absence of renal impairment. Treatment decisions, including regarding the dose reduction of chemotherapy agents, were made in treatment meetings held at each department.

The treatment response was assessed using gadolinium-enhanced MRI after induction therapy and consolidation therapy and was defined as a complete response (CR) or partial response (PR) (9). The tumor burden was estimated using the sum of the products of the longest perpendicular diameters (SPD), which was calculated by multiplying the two longest perpendicular diameters for up to five target lesions. Adverse events were classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Adverse events were assessed during MTX-based induction therapy. Since it is not possible to determine adverse events per treatment for leukoencephalopathy, the adverse event rate for leukoencephalopathy was calculated for the entire course of treatment.

Assessment of MTX-based therapy. The dosage, number of courses, and adverse events were evaluated for high-dose MTX-based therapy, including R-MTX and R-MPV. The RDI of MTX was calculated as the ratio of the delivered dose of MTX to the reference dose per unit of time. The reference dose intensity was based on 3.5 g/m^2 MTX being administered every 2 weeks. For patients in whom the high-dose MTX regimen was discontinued, the RDI was calculated based on the number of courses administered. The relative treatment intensity of MTX was calculated by multiplying the RDI of MTX by the number of MTX-based chemotherapy courses, as previously reported in a study of older DLBCL patients based on relative treatment intensity (10). For example, if three courses of MTX involving a dose of 3.5 g/m^2 were administered every two weeks without postponement, the relative treatment intensity for MTX would be three. Delayed MTX clearance was defined as a serum MTX concentration of ≥0.1 mmol/l at 72 h after the start of the high-dose MTX therapy.

Statistical analyses. Bivariate analyses of categorical variables were conducted using Fisher's exact test. To analyze continuous variables, the Mann-Whitney U-test or Student's unpaired t-test was used. The primary endpoint was overall survival (OS). The secondary endpoint was progression-free survival (PFS). OS was calculated from diagnosis to death or the last follow-up. PFS was calculated from disease progression, relapse, death, or the last follow-up. OS and PFS were estimated using the Kaplan-Meier method and were compared

Table I. Patient characteristics.

Characteristic	Total (n=26)	Neurosurgery (n=15)	Hematology/oncology (n=11)	P-value
Date of initial treatment	Jan. 2011-Dec. 2021	Jan. 2011-Mar. 2018	Apr. 2018-Dec. 2021	
Median age, years (range)	62 (31-83)	65 (31-72)	62 (48-83)	0.38
Male, n (%)	18 (69)	11 (73)	7 (63)	0.68
ECOG PS ≥2, n (%)	15 (58)	10 (67)	5 (46)	0.43
KPS <70, n (%)	11 (42)	7 (47)	4 (37)	0.70
MSKCC prognostic model, n (%)				0.65
Class 1	4 (16)	3 (20)	1 (9)	
Class 2	11 (42)	5 (33)	6 (55)	
Class 3	11 (42)	7 (47)	4 (36)	
IELSG prognostic model, n (%)				0.26
Low	7 (27)	5 (33)	2 (18)	
Intermediate	9 (35)	3 (20)	6 (55)	
High	10 (38)	7 (47)	3 (27)	
CSF infiltration, n (%)		0 (0)	2 (18)	0.17
Intraocular infiltration, n (%)	4 (16)	1 (6)	3 (27)	0.28
EGFR, mean (range)	81.3 (49.8-109.4)	86.7 (56.3-107.6)	73.9 (49.8-109.4)	0.056
Induction therapy, n (%)				<0.001
HD-MTX	15 (58)	15 (0)	0 (0)	
R-MTX	3 (12)	0 (0)	3 (27)	
R-MPV	8 (30)	0 (0)	8 (73)	
Consolidation therapy, n (%)				<0.001
WBRT	11 (42)	11 (73)	0 (0)	
WBRT and HD-AraC	2 (8)	0 (0)	2 (18)	
ASCT	3 (11)	0 (0)	3 (27)	
Tirabrutinib	2 (8)	0 (0)	2 (18)	
Local RT	1 (4)	0 (0)	1 (10)	
None	7 (27)	4 (27)	3 (27)	

ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; KPS, Karnofsky Performance Status; MSKCC, Memorial Sloan-Kettering Cancer Center; IELSG, International Extranodal Lymphoma Study Group; CSF, cerebrospinal fluid; EGFR, estimated glomerular filtration rate; HD-MTX, high-dose methotrexate; R-MTX, rituximab and HD-MTX; R-MPV, rituximab, HD-MTX, procarbazine, and vincristine; WBRT, whole-brain radiotherapy; HD-AraC, high-dose cytarabine; ASCT, autologous stem cell transplantation; RT, radiotherapy.

using the log-rank test. Data were censored at the date of the last follow-up or September 30, 2022. The Cox proportional hazards regression model was used in the univariate and multivariate analyses of PFS. Clinical factors that exhibited P-values of <0.20 in the univariate analyses were subjected to multivariate analysis and selected in a stepwise-deleted manner. The stepwise method allows the automatic inclusion and exclusion of variables based on their significance levels (P-values). Age was divided into two groups; over and under 60 years old. The consolidation therapies described in Table I were divided into three groups: radiotherapy, chemotherapy, and none. The chemotherapy group included the patients treated with whole-brain radiotherapy (WBRT) combined with high-dose cytarabine (HD-Ara-C), autologous stem cell transplantation (ASCT) following high-dose chemotherapy, or tirabrutinib. The grades of adverse events were also assessed. P<0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using the EZR software package, version 1.55 (Jichi Medical University Saitama Medical Center, Saitama, Japan), or GraphPad PRISM, version 9 (San Diego, CA, USA) (11).

Results

Patient characteristics. Twenty-six patients were analyzed. There were 15 (58%) and 11 (42%) patients in the neurosurgery and hematology/oncology groups, respectively. The clinical characteristics of each group are summarized in Table I. The median age of all patients at diagnosis was 62 years (range: 31-83). Eleven patients (42%) presented with a Karnofsky Performance Status (KPS) of <70. According to the MSKCC prognostic model, 4 (16%) and 11 (42%) patients were classified into classes 1 and 2, respectively. Age did not differ significantly between the neurosurgery and hematology/oncology groups (P=0.38). In addition, there was no significant difference in the distribution of the MSKCC or IELSG prognostic scores between the two groups. The mean estimated glomerular filtration rate (eGFR) before the initial

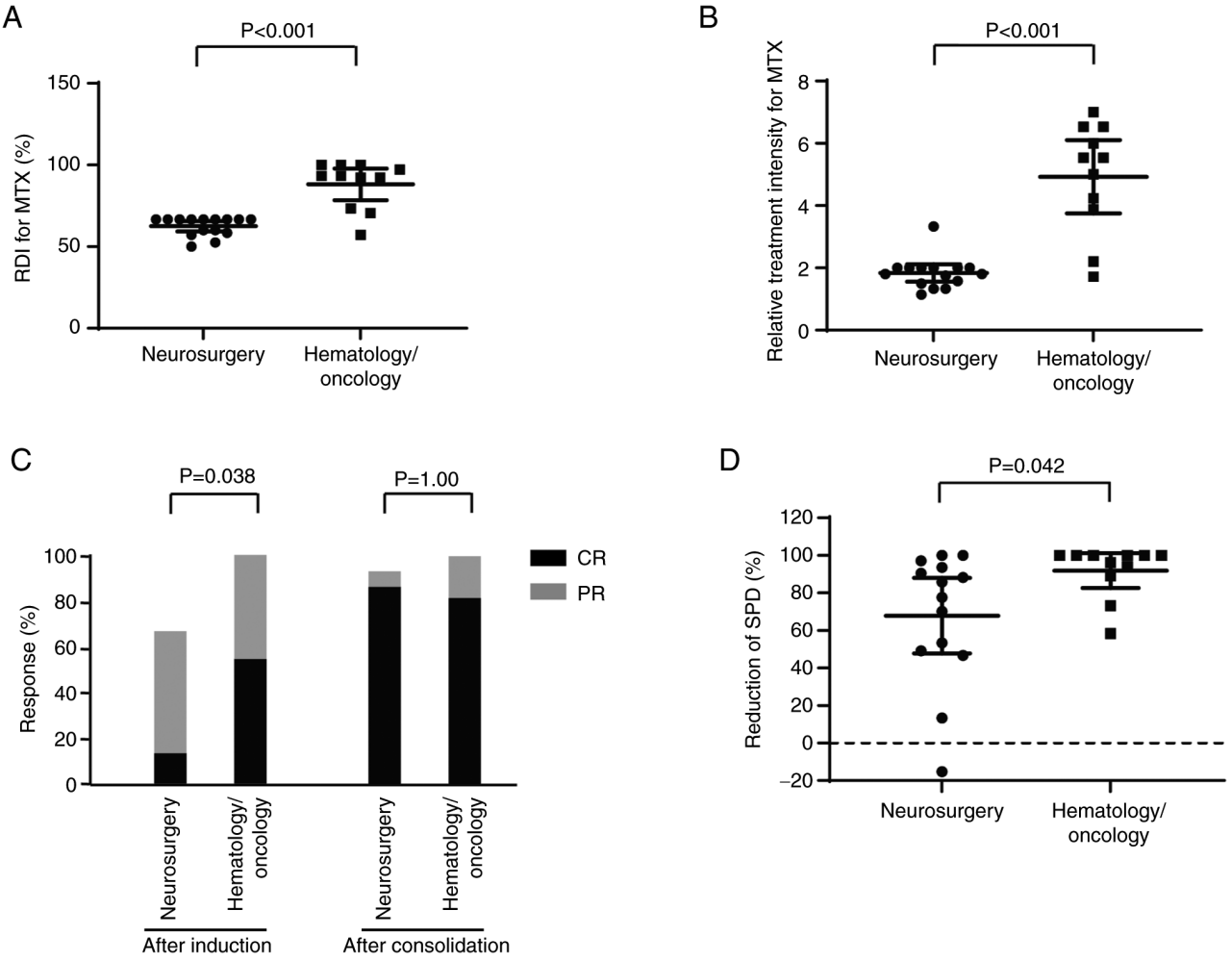

Figure 1. (A) RDI of methotrexate during induction therapy according to the treating department. Error bars represent 95% CI. (B) Relative treatment intensity of MTX during induction therapy. (C) Response rate after induction and consolidation therapies. Bars represent the overall response rate and have been divided into CR and PR. P-values were obtained using Fisher's exact test during comparisons of the CR rate between the neurosurgery and hematology/oncology departments. (D) Rate of reduction in the sum of the products of the SPD. Negative values indicate an increase in tumor size. The error bars represent 95% CI. RDI, relative dose intensity; MTX, methotrexate; CI, confidence intervals; CR, complete response; PR, partial response; SPD, sum of the products of the longest perpendicular diameter.

treatment was 81.3 ml/min/1.73 m^2 (range: 49.8-109.4) for all patients. Although the difference was not significant, the patients treated at the hematology/oncology department tended to have lower eGFR than those treated at the neurosurgery department (P=0.056).

Treatments administered at each department. Different treatment strategies were followed at each department (Fig. S1). All treatment plans were discussed at departmental meetings. The treatment regimens administered as induction and consolidation therapies at each department are summarized in Table I. In this study, three types of high-dose MTX-based regimens were administered to PCNSL patients as induction therapies. All PCNSL patients treated at the neurosurgery department received the high-dose MTX regimen. In the hematology/oncology department, 3 (27%) and 8 (73%) patients received the R-MTX and R-MPV regimens, respectively.

After achieving a CR or PR, the patients received consolidation therapy. At the neurosurgery department, 11 patients (73%) were treated with WBRT as consolidation therapy. On the other hand, two patients (18%) received WBRT at the hematology/oncology department. In these two cases, one patient's dose of WBRT was reduced, and a high-dose cytarabine (Ara-C) regimen was administered to both patients (8). The proportion of patients who received WBRT as consolidation therapy was significantly lower among the patients treated at the hematology/oncology department than among those treated at the neurosurgery department (P=0.045).

At the hematology/oncology department, 3 patients (27%) received high-dose chemotherapy and underwent autologous hematopoietic stem cell transplantation (auto-HSCT). The high-dose chemotherapy regimen included intravenous busulfan and thiotepa at previously reported doses (12). Two patients who could not continue receiving the high-dose MTX regimen after achieving a PR due to toxicities caused by the chemotherapy were treated with oral tirabrutinib, a second-generation Bruton's tyrosine kinase (BTK) inhibitor, as consolidation or maintenance therapy at the hematology/oncology department (13).

The treatments administered after relapse or progression are shown in Fig. S2. At the neurosurgery department, 4 patients underwent retreatment with the high-dose MTX regimen. One

Table II. Univariate and multivariate analyses of the factors associated with progression-free survival.

	Univariate		Multivariate	
Factor	HR (95%CI)	P-value	HR (95%CI)	P-value
Age ≥60 years	2.37 (0.50-11.2)	0.28		
Female sex	0.34 (0.069-1.63)	0.18		
KPS <70	3.04 (0.79-11.7)	0.045	4.85 (1.02-23.0)	0.047
Induction therapy	0.36 (0.11-1.19)	0.094		
Consolidation therapy	0.50 (0.18-1.37)	0.18		
Neurosurgery department	7.08 (0.88-57.2)	0.066	9.61 (1.14-81.1)	0.038

HR, hazard ratio; CI, confidence interval; KPS, Karnofsky Performance Status.

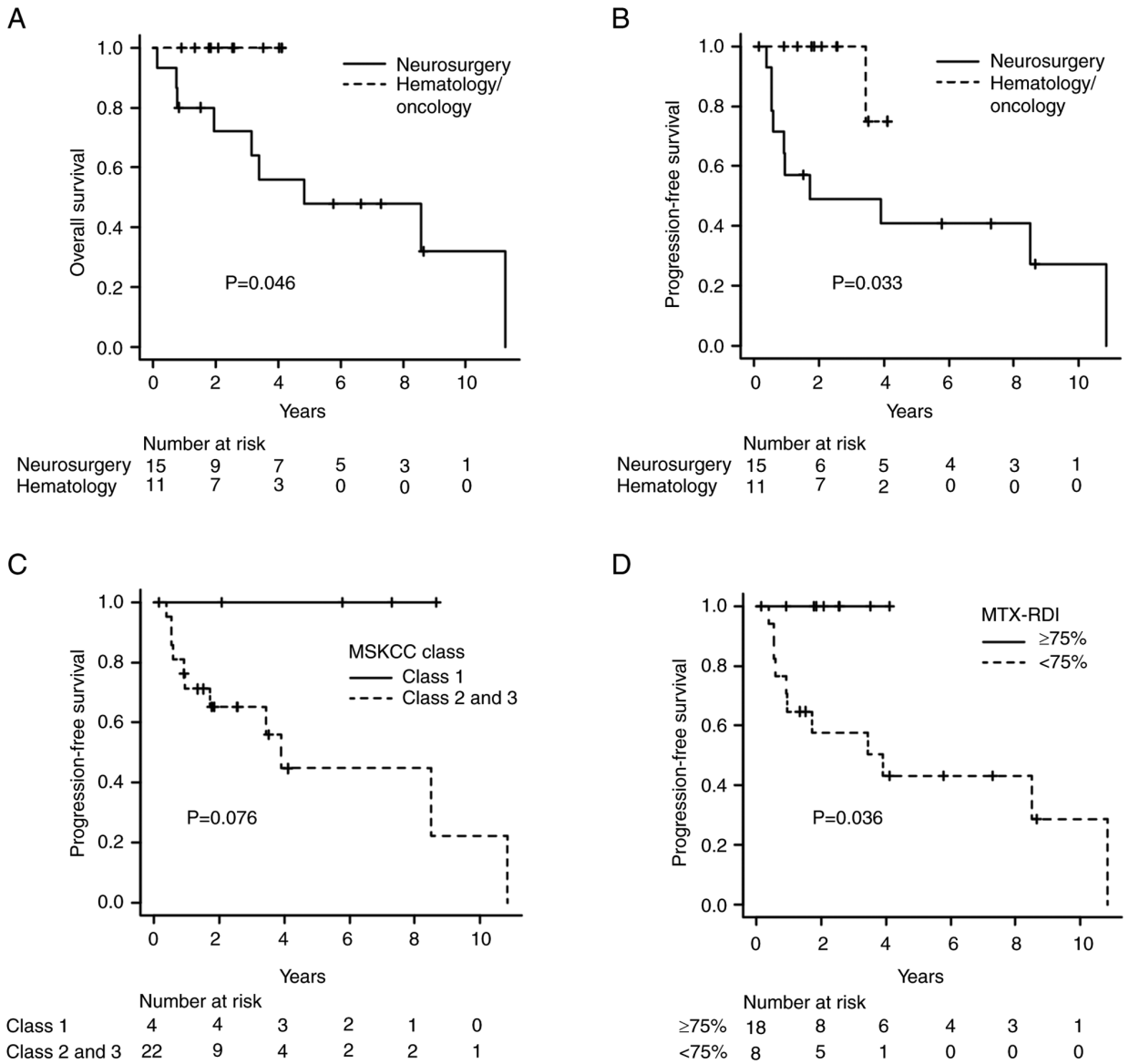

Figure 2. (A) Overall survival according to the treating department. Progression-free survival according to (B) treating department, (C) MSKCC prognostic model and (D) MTX-RDI. MSKCC, Memorial Sloan-Kettering Cancer Center; MTX-RDI, relative dose intensity of methotrexate.

of the patients treated at the hematology/oncology department developed a relapse in their eye and was treated with radiotherapy (delivered to the ocular lesion) and oral tirabrutinib without further recurrence.

Table III. Adverse events related to the high-dose MTX-based regimen.

	Neurosurgery department				Hematology/oncology department				P-value	
Toxicity	All grades (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)	All grades	Grade 3-5
Leukopenia	6 (40)	2 (13)	0 (0)	0 (0)	10 (91)	6 (55)	0 (0)	0 (0)	0.014	0.038
Neutropenia	6 (40)	1 (7)	0 (0)	0 (0)	10 (91)	3 (27)	0 (0)	0 (0)	0.014	0.28
Anemia	5 (33)	1 (7)	0 (0)	0 (0)	10 (91)	3 (27)	0 (0)	0 (0)	0.0052	0.28
Thrombocytopenia	3 (20)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.24	1.00
Oral mucositis	1 (7)	0 (0)	0 (0)	0 (0)	2 (18)	0 (0)	0 (0)	0 (0)	0.56	1.00
Hepatic toxicity	9 (60)	1 (7)	0 (0)	0 (0)	7 (64)	1 (9)	0 (0)	0 (0)	1.00	1.00
Renal toxicity	1 (7)	0 (0)	0 (0)	0 (0)	3 (27)	0 (0)	0 (0)	0 (0)	0.28	1.00
Pneumonia	2 (13)	1 (7)	0 (0)	1 (7)	2 (18)	2 (18)	0 (0)	0 (0)	1.00	1.00
Infection other than pneumonia	4 (27)	0 (0)	0 (0)	0 (0)	2 (18)	0 (0)	0 (0)	0 (0)	1.00	1.00
Deep vein thrombosis	0 (0)	0 (0)	0 (0)	0 (0)	3 (27)	3 (27)	0 (0)	0 (0)	0.064	0.064
Leukoencephalopathy[a]	14 (93)	3 (20)	0 (0)	0 (0)	7 (63)	0 (0)	0 (0)	0 (0)	0.13	0.24

[a]Leukoencephalopathy was assessed based on the entire course of treatment. MTX, methotrexate.

MTX treatment delivery. The median number of high-dose MTX courses administered was 3 (range: 2-5) and 6 (range: 3-7) in the neurosurgery and hematology/oncology groups, respectively. The initial dose of MTX administered was 3.5 g/m^2 for all patients treated at the neurosurgery department. On the other hand, 3 (27%) of the patients treated at the hematology/oncology department had their initial MTX doses reduced, with two patients receiving 2 g/m^2 and one receiving 3 g/m^2. The median volume of supplemental fluid required for hydration was 3,000 ml (in all patients) and 2,000 ml (range: 1,500-3,000) in the patients treated at the neurosurgery and hematology/oncology departments, respectively. At both departments, the fluid used for hydration included sodium bicarbonate to alkalize the patients' urine. Urinary pH was monitored in the patients treated at the hematology/oncology department, and sodium bicarbonate was added if a patient's urinary pH fell below 7.0. Acetazolamide was administered regularly for diuresis to the patients treated at the hematology/oncology department. Among the patients treated at the neurosurgery department, delayed MTX clearance was observed in 33 of 44 (75%) high-dose MTX courses. In the hematology/oncology department, delayed MTX clearance occurred in 22 of 60 (37%) high-dose MTX-based courses, which was significantly less frequent than was seen in the patients treated at the neurosurgery department (P<0.001). The median RDI of MTX was 67% (50-67) and 93% (57-100) in the neurosurgery and hematology/oncology groups, respectively (P<0.001, Fig. 1A). The mean relative treatment intensity of MTX was significantly higher in the hematology/oncology group than in the neurosurgery group (1.8 vs. 4.9, P<0.001, Fig. 1B).

Response rate. The response rates after induction and consolidation therapy were assessed. The overall response rate to high-dose MTX-based induction therapy was 81% among all patients. The CR rate after induction therapy was 13 and 55% in the neurosurgery and hematology/oncology groups, respectively (Fig. 1C). The proportion of patients that achieved a CR after high-dose MTX-based therapy was significantly higher in the hematology/oncology group than in the neurosurgery group (P=0.038). After consolidation therapy, including WBRT, there was no significant difference in the CR rate between the two groups (neurosurgery group: 87% vs. hematology/oncology group: 82%, P>0.999, Fig. 1C). The tumor volume reduction rate, as determined by measuring the SPD, after high-dose MTX-based therapy was significantly higher in the hematology/oncology group than in the neurosurgery group (P=0.042, Fig. 1D).

Survival analysis. Among all patients, the median duration of the follow-up period was 2.9 years (range: 0.1-11.3). There was no significant difference in the duration of the follow-up period between the neurosurgery and hematology/oncology groups (median: 3.4 vs. 2.5 years, respectively; P=0.45). The estimated two-year OS and PFS rates of all patients were 83.3% [95% confidence interval (CI): 60.9-93.5] and 71.1% (95%CI: 48.5-85.1), respectively. The OS rate for the patients treated at the hematology/oncology department was significantly higher than that for those treated at the neurosurgery department (two-year OS, neurosurgery group: 72%

vs. hematology/oncology group: 100%; P=0.046, Fig. 2A). The two-year PFS rate was 49 and 100% in the neurosurgery and hematology/oncology groups, respectively (P=0.033, Fig. 2B). Although the difference was not significant, the patients in classes 2 and 3 according to the MSKCC prognostic model tended to have worse OS and PFS rates than those in class 1 (PFS: P=0.076, Figs. 2C and S3). The PFS rate was significantly higher in the patients in whom an MTX RDI of ≥75% was achieved than in those in whom the RDI of MTX was <75% (P=0.036, Fig. 2D). Seven patients died from relapse during the study observation period. One of the patients treated at the neurosurgery department died of pneumonia (a case of treatment-related mortality) during induction therapy. None of the patients treated at the hematology/oncology department suffered treatment-related mortality during induction or consolidation therapy, including auto-HSCT.

Multivariate analysis was performed to evaluate the factors that affected survival, including the types of induction and consolidation therapies. Due to the small number of deaths available for the analysis of OS, multivariate analysis of the factors that affected PFS was conducted instead. A higher KPS and being treated at the neurosurgery department were found to be associated with an increased risk of relapse (Table II).

Toxicities. The toxicities of the high-dose MTX-based induction therapy are summarized in Table III. The incidence of cytopenia, including leukopenia, neutropenia, and anemia, was higher in the hematology/oncology group than in the neurosurgery group. However, there was no significant difference in the incidence of infections, including pneumonia, between the two departments. Although the difference was not significant, the incidence of leukoencephalopathy tended to be higher among the patients treated at the neurosurgery department who received WBRT after high-dose MTX therapy.

Discussion

The optimal induction and consolidation therapies for PCNSL have not been established. Therefore, the treatment options employed may vary depending on the treating department. In this study, the outcomes of PCNSL patients treated at our hematology/oncology department were better than those of PCNSL patients treated at our neurosurgery department. The patients treated at the hematology/oncology department received combination therapy for the induction regimen, and their treatment involved a higher RDI of MTX. The number of high-dose MTX-based courses also differed, resulting in a higher relative treatment intensity for MTX in the hematology/oncology group. A higher CR rate and a more significant reduction in the SPD were achieved after induction therapy in the hematology/oncology group than in the neurosurgery group. For consolidation therapy, the patients treated at the neurosurgery department only received WBRT, while those treated at the hematology/oncology department received a variety of therapies, including auto-HSCT and tirabrutinib maintenance therapy.

PCNSL is a hematological malignancy. Hematological malignancies are sensitive to chemotherapy, and sufficiently intensive chemotherapy may improve the outcomes of patients with hematological malignancies. Treating-department-related differences in outcomes have been reported in the treatment of AYA with ALL. Among AYA with ALL, the patients treated with pediatric protocols exhibited better outcomes than those treated with adult protocols (14,15). Pediatric protocols include greater cumulative doses of steroids, vincristine, and L-asparaginase. In addition to differences in protocol design and dose intensity, potential variations in the degree of adherence to the scheduled drug treatment outlined in the chosen treatment protocol between pediatric and adult oncologists may also affect outcomes (2,16). In the latter studies, treatment by adult oncologists tended to be more spaced out between chemotherapy courses than treatment by pediatric oncologists, which led to differences in treatment intensity. In our study, comparing the outcomes of PCNSL patients treated at the hematology/oncology department with those of PCNSL patients treated at the neurosurgery department, we found differences in the relative dose and treatment intensity of MTX during induction therapy and in the choices of consolidation therapy.

The RDI is an indicator of the intensity of chemotherapy (17). It has been reported to have an important impact on survival outcomes in DLBCL patients treated with R-CHOP-based chemotherapy (3,4). The RDI of MTX was also reported to have a prognostic impact in PCNSL patients (5). The latter study demonstrated that an MTX RDI of >75% was associated with increased OS. However, no previous studies used the RDI of MTX to compare treatment intensity across treating departments. In our study, the patients treated at the hematology/oncology department received HD-MTX at a higher RDI of MTX and achieved better OS. In addition to the differences in RDI, the number of courses administered also differed between the two departments. A previous study of DLBCL suggested that relative treatment intensity may be valuable for assessing treatment intensity in retrospective studies in which different numbers of chemotherapy courses were administered (10). In this study, the PCNSL patients treated at the hematology/oncology department received high-dose MTX therapies at significantly higher treatment intensities than those treated at the neurosurgery department. Moreover, 63% of the patients in the hematology/oncology group received combined treatment with high-dose MTX and an alkylating agent. Some alkylating agents exhibit high CNS bioavailability (18). Furthermore, the addition of rituximab to MTX-based chemotherapy can improve survival, particularly when the blood-brain barrier is disrupted (1). The combination of high-dose MTX with other agents, including alkylating agents and rituximab, increases the treatment intensity and improves the treatment response (1,19,20). Differences in treatment intensity during induction therapy may affect CR rates and outcomes in addition to MTX dose intensity.

The consolidation therapies for PCNSL vary and include WBRT, high-dose non-myeloablative chemotherapy, myeloablative chemotherapy with auto-HSCT, medical maintenance, and observation. WBRT was used as the basis of such treatment in the past. Recently, myeloablative chemotherapy with auto-HSCT was reported to be effective as a consolidation therapy, especially in PCNSL patients aged 60 years or younger (21,22). However, auto-HSCT requires special equipment for hematopoietic stem cell harvesting and preservation and medical staff who specialize in stem cell collection and transplantation. In neurological diseases other

than PCNSL, there are no indications for auto-HSCT, while in hematological disease auto-HSCT is the standard treatment for relapsed malignant lymphoma and initially-diagnosed multiple myeloma. However, treatment experience may influence treatment decisions. In a retrospective study conducted in a neurosurgery department, no patients received auto-HSCT as a consolidation therapy (23). Some patients treated at our hematology/oncology department received BTK inhibitors as consolidation therapy, especially patients who could not continue receiving treatment with cytotoxic agents due to their frailty (13). Different treatment departments have different specialties, and different hospital settings have been reported to lead to different treatment patterns (24). In addition to differences in the RDI of MTX in induction therapy, differences in the treatment options available for consolidation therapy may affect the outcomes of PCNSL patients.

This study had several limitations. First, it was a single-center retrospective study. The treatments employed for PCNSL may vary according to the treating hospital and country. The MATRix regimen, which includes thiotepa, is widely used for induction therapy. However, in Japan thiotepa is not covered by the national health insurance system, except for use during auto-HSCT. In this study, the induction therapy did not include thiotepa. Second, the treatment era differed between the neurosurgery and hematology/oncology groups. Until March 2018, PCNSL was diagnosed by the neurosurgery department, and the same department managed the initial treatment. However, combination chemotherapy after relapse was administered by the hematology department. In 2018, discussions between the two departments concluded that greater consistency between the initial treatments and the treatments administered for relapsed disease was desirable. As a result, the hematology department has also been responsible for the initial treatment since April 2018. Although the types of induction and consolidation therapies were not found to be significantly related to the risk of relapse in the multivariate analysis, the differences between the treatment eras may still have affected the results due to advances in supportive care and other factors. Third, the treatment intensity of the induction therapies was assessed based on the RDI of MTX; therefore, the analysis did not include changes in treatment intensity due to the use of combinations of chemotherapy agents. Patients treated at an MTX RDI of ≥75% tended to receive combination chemotherapies as induction therapies (Table SI). Although prospective comparative studies of the additional therapies used in conjunction with MTX are lacking, the use of MTX in combination with other alkylators, including procarbazine, is recommended (1,25). In addition to the MTX RDI, combination therapy may have contributed to the increased intensity of induction therapy at our hematology/oncology department.

In conclusion, the PCNSL patients treated at our hematology/oncology department had better outcomes than those treated at our neurosurgery department, although it should be noted that these groups were treated in different periods. The higher RDI of MTX and use of combination therapies during induction therapy may have been responsible for the better prognoses seen in the patients treated at the hematology/oncology department. As with the differences in outcomes observed between pediatrics and hematology departments for AYA with ALL, the treatment outcomes of PCNSL patients may differ between neurosurgery and hematology/oncology departments. Further multicenter studies are warranted to elucidate the outcomes of PCNSL patients treated at neurosurgery and hematology/oncology departments.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HH designed the study, acquired, analyzed and interpreted the data, and wrote the original manuscript. TO designed the study, acquired and interpreted the data, and critically revised the manuscript. JF, YH, SM and TM acquired and analyzed the data and critically revised the manuscript. NN and TS designed the study, critically revised the manuscript and supervised the study. HH and TO confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the ethics committee of Wakayama Medical University (approval no. 3629). All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the relevant institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained in the form of opt-out via a website.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Schaff LR and Grommes C: Primary central nervous system lymphoma. Blood 140: 971-979, 2022.
2. Stock W: Adolescents and young adults with acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2010: 21-29, 2010.
3. Hirakawa T, Yamaguchi H, Yokose N, Gomi S, Inokuchi K and Dan K: Importance of maintaining the relative dose intensity of CHOP-like regimens combined with rituximab in patients with diffuse large B-cell lymphoma. Ann Hematol 89: 897-904, 2010.

4. Bataillard EJ, Cheah CY, Maurer MJ, Khurana A, Eyre TA and El-Galaly TC: Impact of R-CHOP dose intensity on survival outcomes in diffuse large B-cell lymphoma: A systematic review. Blood Adv 5: 2426-2437, 2021.
5. Farhi J, Laribi K, Orvain C, Hamel JF, Mercier M, Galy AS, Clavert A, Rousselet MC, Tanguy-Schmidt A, Hunault-Berger M and Moles-Moreau MP: Impact of front line relative dose intensity for methotrexate and comorbidities in immunocompetent elderly patients with primary central nervous system lymphoma. Ann Hematol 97: 2391-2401, 2018.
6. Ferreri AJ, Blay JY, Reni M, Pasini F, Spina M, Ambrosetti A, Calderoni A, Rossi A, Vavassori V, Conconi A, *et al*: Prognostic scoring system for primary CNS lymphomas: The international Extranodal lymphoma study group experience. J Clin Oncol 21: 266-272, 2003.
7. Abrey LE, Ben-Porat L, Panageas KS, Yahalom J, Berkey B, Curran W, Schultz C, Leibel S, Nelson D, Mehta M and DeAngelis LM: Primary central nervous system lymphoma: The Memorial Sloan-Kettering cancer center prognostic model. J Clin Oncol 24: 5711-5715, 2006.
8. Morris PG, Correa DD, Yahalom J, Raizer JJ, Schiff D, Grant B, Grimm S, Lai RK, Reiner AS, Panageas K, *et al*: Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: Final results and long-term outcome. J Clin Oncol 31: 3971-3979, 2013.
9. Abrey LE, Batchelor TT, Ferreri AJ, Gospodarowicz M, Pulczynski EJ, Zucca E, Smith JR, Korfel A, Soussain C, DeAngelis LM, *et al*: Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol 23: 5034-5043, 2005.
10. Hiroi T, Hosoi H, Kuriyama K, Murata S, Morimoto M, Mushino T, Nishikawa A, Tamura S and Sonoki T: An evaluation based on relative treatment intensity in older patients treated with reduced-dose R-THP-COP therapy for diffuse large B-cell lymphoma: A multicenter retrospective cohort study. J Geriatr Oncol 14: 101396, 2023.
11. Kanda Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48: 452-458, 2013.
12. Kondo E, Ikeda T, Goto H, Nishikori M, Maeda N, Matsumoto K, Kitagawa H, Noda N, Sugimoto S and Hara J: Pharmacokinetics of thiotepa in high-dose regimens for autologous hematopoietic stem cell transplant in Japanese patients with pediatric tumors or adult lymphoma. Cancer Chemother Pharmacol 84: 849-860, 2019.
13. Okamura T, Hosoi H, Matsufusa T, Akagi Y, Iwamoto R, Kosako H, Murata S, Mushino T, Murata SI and Sonoki T: Tirabrutinib maintenance therapy for a patient with high-dose methotrexate-ineligible primary central nervous system lymphoma. Ann Hematol 101: 1379-1381, 2022.
14. Boissel N, Auclerc MF, Lheritier V, Perel Y, Thomas X, Leblanc T, Rousselot P, Cayuela JM, Gabert J, Fegueux N, *et al*: Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. J Clin Oncol 21: 774-780, 2003.
15. Stock W, La M, Sanford B, Bloomfield CD, Vardiman JW, Gaynon P, Larson RA and Nachman J; Children's Cancer Group; Cancer and Leukemia Group B studies: What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of children's cancer group and cancer and leukemia group B studies. Blood 112: 1646-1654, 2008.
16. Schiffer CA: Differences in outcome in adolescents with acute lymphoblastic leukemia: A consequence of better regimens? Better doctors? Both? J Clin Oncol 21: 760-761, 2003.
17. Lepage E, Gisselbrecht C, Haioun C, Sebban C, Tilly H, Bosly A, Morel P, Herbrecht R, Reyes F and Coiffier B: Prognostic significance of received relative dose intensity in non-Hodgkin's lymphoma patients: Application to LNH-87 protocol. The GELA (Groupe d'Etude des Lymphomes de l'Adulte). Ann Oncol 4: 651-656, 1993.
18. Ferreri AJ, Cwynarski K, Pulczynski E, Ponzoni M, Deckert M, Politi LS, Torri V, Fox CP, Rosée PL, Schorb E, *et al*: Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: Results of the first randomisation of the international Extranodal lymphoma study group-32 (IELSG32) phase 2 trial. Lancet Haematol 3: e217-227, 2016.
19. Kasenda B, Ferreri AJ, Marturano E, Forst D, Bromberg J, Ghesquieres H, Ferlay C, Blay JY, Hoang-Xuan K, Pulczynski EJ, *et al*: First-line treatment and outcome of elderly patients with primary central nervous system lymphoma (PCNSL)-a systematic review and individual patient data meta-analysis. Ann Oncol 26: 1305-1313, 2015.
20. Hoang-Xuan K, Bessell E, Bromberg J, Hottinger AF, Preusser M, Rudà R, Schlegel U, Siegal T, Soussain C, Abacioglu U, *et al*: Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: Guidelines from the European association for neuro-oncology. Lancet Oncol 16: e322-332, 2015.
21. Ferreri AJM, Cwynarski K, Pulczynski E, Fox CP, Schorb E, La Rosée P, Binder M, Fabbri A, Torri V, Minacapelli E, *et al*: Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: Results of the second randomisation of the international Extranodal lymphoma study group-32 phase 2 trial. Lancet Haematol 4: e510-e523, 2017.
22. Houillier C, Taillandier L, Dureau S, Lamy T, Laadhari M, Chinot O, Moluçon-Chabrot C, Soubeyran P, Gressin R, Choquet S, *et al*: Radiotherapy or autologous stem-cell transplantation for primary CNS lymphoma in patients 60 years of age and younger: Results of the intergroup ANOCEF-GOELAMS randomized phase II PRECIS study. J Clin Oncol 37: 823-833, 2019.
23. Sasaki N, Kobayashi K, Saito K, Shimizu S, Suzuki K, Lee J, Yamagishi Y, Shibahara J, Takayama N, Shiokawa Y and Nagane M: Consecutive single-institution case series of primary central nervous system lymphoma treated by R-MPV or high-dose methotrexate monotherapy. Jpn J Clin Oncol 50: 999-1008, 2020.
24. Patel AM, Ali O, Kainthla R, Rizvi SM, Awan FT, Patel T, Pan E, Maher E, Desai NB, Timmerman R, *et al*: Primary central nervous system lymphoma: A real-world comparison of therapy access and outcomes by hospital setting. Neurooncol Pract 9: 183-192, 2022.
25. Calimeri T, Steffanoni S, Gagliardi F, Chiara A and Ferreri AJM: How we treat primary central nervous system lymphoma. ESMO Open 6: 100213, 2021.