ORIGINAL

Continued-Maintenance Therapy with High-dose Methotrexate Improves Overall Survival of Patients with Primary Central Nervous System Lymphoma

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Abstract : *Background.* PCNSL is mainly treated with HD-MTX-based chemotherapy with or without WBRT. However, As WBRT is associated with delayed neurotoxicity leading to dementia in the elderly, many institutes reported benefits of intensive chemotherapy or high-dose chemotherapy with ASCT. We investigated whether treatment with HD-MTX and rituximab, followed by continued-maintenance HD-MTX monotherapy (3.5g/m^2), improves overall survival (OS). *Methods.* In this retrospective, single-center trial 52 immunocompetent patients with newly diagnosed PCNSL were included. All were treated between January 2005 and December 2017. The controls were 18 patients who, between 2005 and 2011, had received 3 cycles of HD-MTX and then adjuvant treatment with WBRT. In 2011 we started HD-MTX continued-maintenance therapy to treat 34 PCNSL patients. In the induction phase, these patients received HD-MTX every 14 days until a complete response (CR) was observed. When CR was obtained, maintenance therapy with HD-MTX (3.5g/m^2) was delivered every three months. *Results.* In 3-year overall survival (OS) there was a statistically significant difference between the two groups [controls : 33.1% (95%, CI 12.4 - 55.7%) ; maintenance group : 74.9% (95%, CI 55.6 - 86.7%) ($p < 0.02$)]. *Conclusion* : The induction of HD-MTX based chemotherapy followed by continued-maintenance HD-MTX monotherapy improved OS compared with chemoradiotherapy consisting of HD-MTX followed by WBRT. J. Med. Invest. 68 : 286-291, August, 2021

Keywords **:** *malignant lymphoma, methotrexate, maintenance therapy, whole-brain radiotherapy*

INTRODUCTION

Primary central nervous system lymphomas (PCNSLs) are 1 - 4% of all brain tumors(1, 2) ; their incidence is increased in the elderly. No standard of care for patients with PCNSL has been defined. In most institutions, PCNSL is mainly treated by high-dose methotrexate (HD-MTX)-based chemotherapy with or without subsequent whole-brain radiotherapy (WBRT) ; the overall response rate exceeded 50% (1). However, WBRT is associated with delayed neurotoxicity leading to dementia, especially in the elderly (3). Therefore, to defer or avoid WBRT, intensive and high-dose chemotherapy with autologous stem cell support has been delivered (1, 2, 4, 5). However, as these therapies may elicit severe side effects in the elderly, maintenance therapy has been suggested as an alternative (2, 6).

Rituximab, a humanized anti-CD20 monoclonal antibody, is effective in a variety of systemic B-cell lymphomas. Although its efficacy in patients with PCNSL is incompletely understood, it has been added to PCNSL treatment protocols (1, 7).

We investigated whether the induction with HD-MTX and rituximab chemotherapy, followed by continued-maintenance HD-MTX monotherapy improves the overall survival (OS) of PCNSL patients and whether deferring WBRT helps to avoid deterioration in the Karnofsky performance score (KPS).

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PATIENTS AND METHODS

Patients

Between January 2005 and December 2017, we encountered 59 patients with PCNSL. After excluding 7 patients with HIV infection, a creatinine clearance < 60, and lymphoma outside the central nervous system, our study population consisted of 52 immunocompetent patients with newly diagnosed PCNSL. They underwent stereotactic surgery or tumor resection under craniotomy. The diagnosis was based on histological and immunohistochemical findings.

This study was approved by the institutional review board, and written informed consent was waived because of the retrospective design.

Treatment protocols

Between 2005 and 2011, 18 patients (control, group 1) were treated with 3 cycles of HD-MTX [3.5 g/m^2 intravenously (iv) over 3 hr every 2 weeks] ; thereafter they underwent adjuvant WBRT (total dose 40~50Gy). If progressive disesase (PD) was observed, the protocol was stopped and WBRT was performed. (Figure 1)

In 2011 we started HD-MTX continued-maintenance therapy (group 2, n = 34). In the induction phase these patients received HD-MTX therapy every 14 days until complete response (CR) was observed. Then, maintenance therapy with HD-MTX (3.5g/m^2) was delivered every 3 months. If PD was observed during any treatment phase, the protocol was stopped and WBRT was performed. In 2013 we added rituximab (375 mg/m^2) on day 1 of the induction phase. Patient with relapse in the maintenance phase were treated with rituximab and HD-MTX again. When re-challenge chemotherapy was effective, it was continued

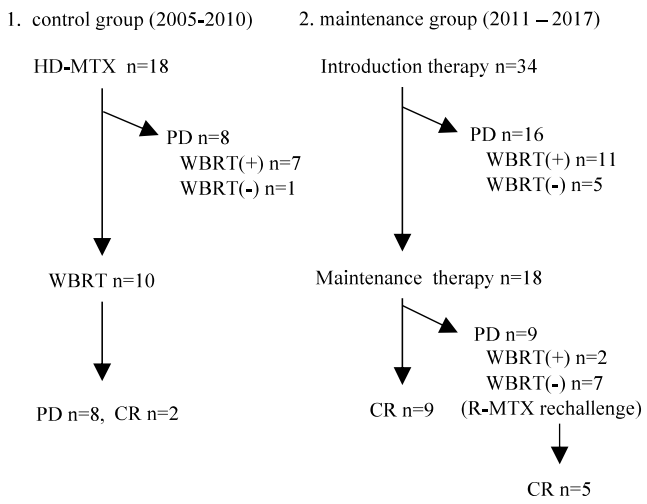

Figure 1. Flow chart summarizing the number of patients in the two treatment groups.
Abbreviations : HD-MTX, high-dose methotrexate ; R-MTX, rituximab plus HD-MTX ; WBRT, whole-brain radiation therapy ; CR, complete response ; PD, progressive disease

until CR was obtained. Maintenance chemotherapy was continued until it failed to elicit a response (Figure 1).

In HD-MTX chemotherapy, leucovorin rescue (15 mg, x 6/day) was administered iv 24 hr after HD-MTX administration. Adequate hydration was maintained. Their urine was alkalized by the iv injection of $NaHCO_3$ and its pH was monitored. These supportive treatments were continued until their plasma MTX level fell to < 0.1 μmol/l.

We defined "protocol-achieved population" as patients obtained CR after three cycles of HD-MTX therapy and WBRT in group 1, and same as patients who obtained CR during the induction phase in group 2.

Response evaluation, toxicity, and performance status

The treatment response was evaluated after each cycle by contrast-enhanced magnetic resonance imaging (CE-MRI). CR was defined as the total disappearance of all enhancing lesions on MRI scans, treatment failure as progressive disease (PD) with an increase of more than 25% in the tumor volume, the observation of new lesions on MRI scans, death, or discontinuation of chemotherapy due to complications. Acute toxicity was evaluated based on the National Cancer Institute's Common Terminology Criteria for Adverse Events. In all patients, the KPS pre-treatment and every 6-months post-treatment was recorded for 2 years.

Statistical analysis

The patient characteristics were compared using Fisher's exact- or the unpaired *t* -test, as appropriate. Progression free survival (PFS) was defined as the interval between the histological diagnosis and tumor progression, overall survival (OS) as the time between the histological diagnosis and death or last follow-up. The Kaplan-Meier method was used for univariate analysis of survival ; differences were assessed with the log-rank test. The Cox proportional hazards regression model was applied to calculate the hazard ratio (HR) and the 95% confidence interval (CI) to investigate prognostic factors for OS. Prognostic candidates were selected with reference to previous studies.

A p value < 0.05 was considered to indicate statistical significance performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) and a modified version of R commander designed to add statistical functions frequently used in biostatistics.

RESULTS

Patient characteristics

Between 2005 and 2017 we encountered 59 patients with B-cell PCNSL ; of these, 52 were entered in our study. Excluded were 7 patients ; 4 due to kidney disturbance, 2 with massive intratumoral hematoma receiving supportive care only, and one with thrombocytopenia.

Of the 52 patients, 18 received HD-MTX and WBRT until 2010 ; they were the control (group 1). The other 34 underwent HD-MTX maintenance therapy ; their treatment was started in 2011 (group 2). In 25 patients of this group, rituximab was added to HD-MTX at the induction phase. As shown in Table 1, the median age, gender, number of lesions, and the KPS at the start of chemotherapy were similar in all 52 patients.

Table 1. Patient demographic and clinical characteristics

Patient characteristics	Control group (group 1)		Maintenance group (group 2)	
	all	Protocol-achieved population	all	Protocol-achieved population
No. of patients	18	10	34	18
Sex				
Male	12	5	15	6
Female	6	5	19	12
Age (years)				
Median	64.5	62.2	68.5	64.8
Range	44 - 77	44-72	38 - 86	38-79
Number of lesions				
Single	6	2	16	7
Multiple	12	8	18	11
KPS at diagnosis				
≧ 70	5	4	12	7
< 70	13	6	22	11

Response and survival

Three cycles of HD-MTX therapy and WBRT were completed by 10 of 18 (55.6%) group 1 patients. In 8, HD-MTX treatment was stopped due to PD (n = 7) and they underwent WBRT ; the other patient developed severe myelosuppression after cycle 3 and died of pneumonia (Figure 1).

Among group 2, 18 of 34 patients (52.9%) who underwent induction- and maintenance therapy obtained CR in the induction phase. The other 16 (47.1%) manifested PD during the induction phase ; 11 received WBRT, 2 suffered rapid tumor progression and did not undergo radiotherapy, 2 were treated with alternative chemotherapy (temozolomide), and one died of pulmonary embolism. Median number of cycles with HD-MTX was 8.8 in group 2, same as in group 1 was 2.9. As shown in Figure 1, 9 of the 34 group 2 patients (26%) manifested PD during the maintenance phase ; 2 underwent WBRT and 7 were re-treated with

HD-MTX plus rituximab. CR was obtained in 5 of the re-challenged patients.

The median follow-up period was 35.6 months (range 3.6 - 140.8 months) in group 1 and 7.9 months (range 0.3 - 87.7 months) in group 2. For group 1, one- and 3-year PFS was 22.9% (95%, CI 6.2 - 45.6%) and 15.2% (95%, CI 2.7 - 37.6%), respectively ; for group 2 it was 39.4% (95%, CI 23.1 - 55.4%) and 32.3% (95%, CI 17.0 - 48.5%), respectively. The inter-group difference was not statistically significant (p=0.07) (Figure. 2).

In all population of group 1, the rate of one- and 3-year OS was 77.8% (95%, CI 51.1 -91.0%) and 33.1% (95%, CI 12.4 - 55.7%), respectively ; it was 88.1% (95%, CI 71.4 - 95.4%) and 74.9% (95%, CI 55.6 - 86.7%), respectively, in the same population of group 2. As the treatment in group 2 was started in 2011, the follow-up period at the time of analysis (2019) was too short to obtain median survival data. There was a statistically significant difference between the groups in OS (log-rank test p=0.02) (Figure 3A) ; in the protocol-achieved population of group 1, 3-year OS was 20.0% (95%, CI 3.1 - 47.5%) ; in the same population of group 2 it was 94.1% (95%, CI 65.0 - 99.1%) (log-rank test p=0.0001) (Figure 3B). Multivariate analysis revealed Receiving maintenance therapy was an independent factor related to OS (HR 0.39 ; 95% CI, 0.17 - 0.90 ; p=0.027). In our study population, well-established prognostic factors such as the patient age and KPS were not associated with OS (Table 2).

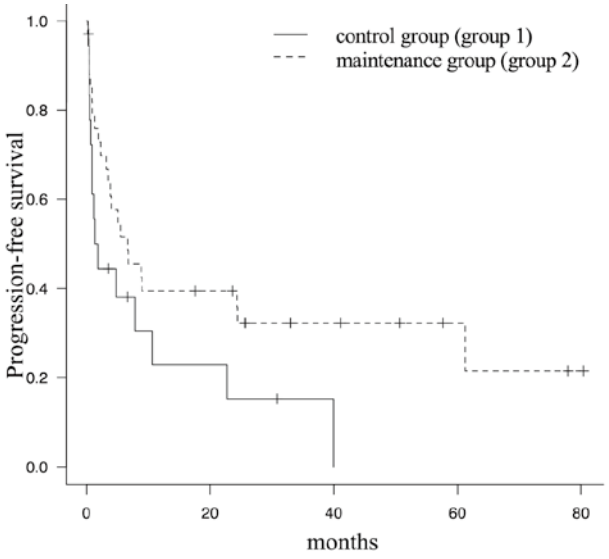

Figure 2. Progression-free survival
Kaplan-Meier curve showing progression-free survival in all patients.
Solid line : control group; dashed line : maintenance group

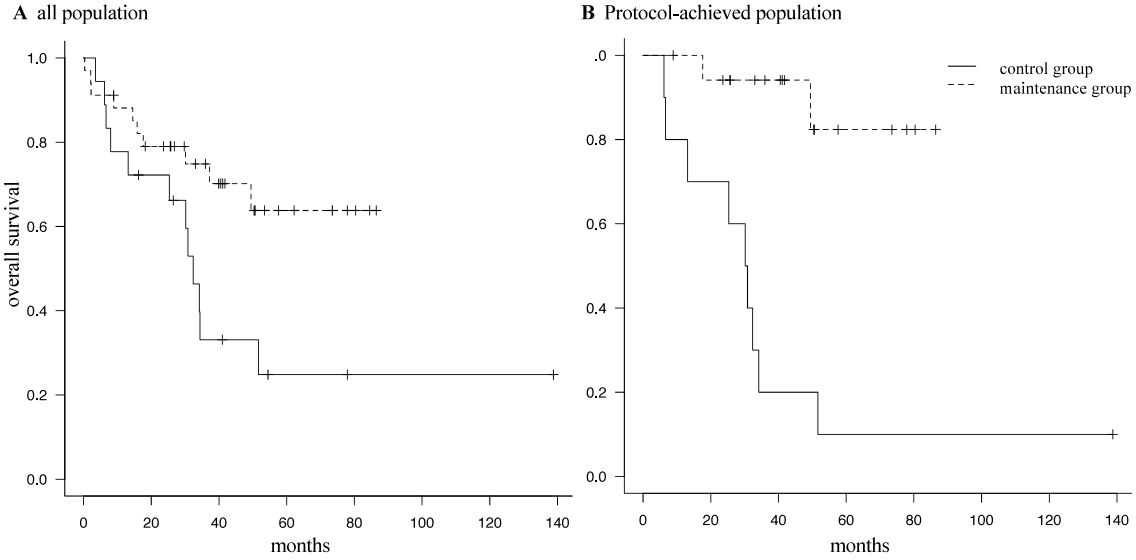

Figure 3. Overall survival
(A) Kaplan-Meier curve showing overall survival in all patients.
(B) Kaplan-Meier curve showing overall survival in protocol-achieved population.
Solid line : control group ; dashed line: maintenance group

Table 2. Univariate and multivariate analyses for overall survival

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	p value	Hazard ratio (95%CI)	p value
Age	1.32 (0.51-3.38)	0.558	1.28 (0.49-3.33)	0.62
KPS	0.72 (0.16-3.12)	0.66	0.68 (0.15-3.02)	0.62
Maintenance therapy	0.39 (0.17-0.92)	0.03	0.39 (0.17-0.90)	0.027

KPS

In all population of group 1, the mean KPS before the start of chemotherapy was 56.7 ; it was 58.3 at 6-, 47.8 at 12-, 46.7 at 18-, and 42.8 at 24 months from the start of chemotherapy. At all time point the range was 0 - 90. In the same population of group 2, the mean KPS before the start of chemotherapy was 57.6 (range 20 - 90) ; it was 64.7 at 6-, 62.6 at 12-, 57.1 at 18-, and 57.1 at 24 months and the range was 0 - 90 at all these time points (Figure 4A).

In the protocol-achieved population of group 2, the KPS was improved 6 months after the start of chemotherapy and remained stable throughout the 24-month observation period. On the other hand, in the same population of group 1, the KPS deteriorated gradually. Although there was no statistically significant inter-group difference, group 2 did not manifest a deterioration in the KPS (Figure 4B).

Toxicity

The rate of toxic effects of grade 3 or higher was 22.2% in group 1 and 14.7% in group 2 ; there was no significant inter-group difference in the toxicity of chemotherapy. One group 1 patient developed severe myelosuppression and died of pneumonia, and 3 developed liver dysfunction reversible without specific therapy. In group 2, one patient died of pulmonary embolism, another developed a wound infection, 2 manifested grade 3 neutropenia, and another 2 developed liver dysfunction.

DISCUSSION

Our findings show that OS in patients who underwent induction with HD-MTX and rituximab chemotherapy, followed by continued-maintenance HD-MTX monotherapy, was superior to OS in patients treated by chemoradiotherapy consisting of 3 cycles of HD-MTX followed by WBRT. Multivariate analysis revealed maintenance therapy as the independent factor for OS and that this treatment avoided KPS deterioration.

No standard of care has been established for PCNSL patients. In the past, PCNSL was treated with WBRT only. In addition to the lack of durable responses, PCNSL patients older than 60 years who received radiotherapy manifested delayed neurotoxicity and deterioration of their KPS (8-10). WBRT alone is no longer initial treatment for most patients with PCNSL.

Recently, PCNSL is mainly treated with HD-MTX based chemotherapy with or without WBRT. Thiel *et al*. (11) performed a phase 3 randomized trial that included 551 PCNSL patients to assess whether HD-MTX-based chemotherapy without WBRT was inferior to the same treatment with WBRT. Patients treated with chemotherapy plus WBRT achieved prolonged PFS but no improvement in OS. Treatment-related neurotoxicity was more common in patients receiving WBRT. Subsequently, various studies have been attempted to defer or avoid WBRT by delivering intensive chemotherapy and high-dose chemotherapy plus autologous stem cell support. In the multicenter phase 2 studies administered multi-agent chemotherapy that included rituximab, MTX, vincristine, and procarbazine for induction therapy that was followed by reduced-dose WBRT and cytarabine as consolidation chemotherapy, intensive chemotherapy was associated with high response rates, long-term disease control, and minimal neurotoxicity (12, 13). In the International Extranodal Lymphoma Study Group-32 trial, an international randomized phase 2 study, patients who reached CR by multi-agent chemotherapy with rituximab, MTX, cytarabine and thiotepa, were randomized into a group that received high-dose chemotherapy supported by autologous stem-cell transplantation (ASCT) and a group treated with HD-MTX followed by WBRT. This study appeared WBRT and ASCT were both feasible and effective as consolidation therapies in patients aged 70 years or younger. However, the incidence of hematologic toxicity was higher in patients who had undergone high-dose chemotherapy supported by ASCT (14). In our study, the incidence of grade 3 and higher toxic effects was 22.2% in the control- and 14.7% in the maintenance group, and those were fewer than intensive chemotherapy.

The effectiveness of HD-MTX continued-maintenance therapy in PCNSL patients has also been evaluated by others (15, 16). Chamberlain *et al*. (17) treated 40 patients with HD-MTX maintenance therapy. They reported a median OS was 33.5 months for 28 patients who completed maintenance therapy. In our maintenance group, OS at 1- and 3 years was 88.1% and 74.9%, respectively. These outcomes were similar to patients who received multi-agent chemotherapy in earlier studies (Table 3).

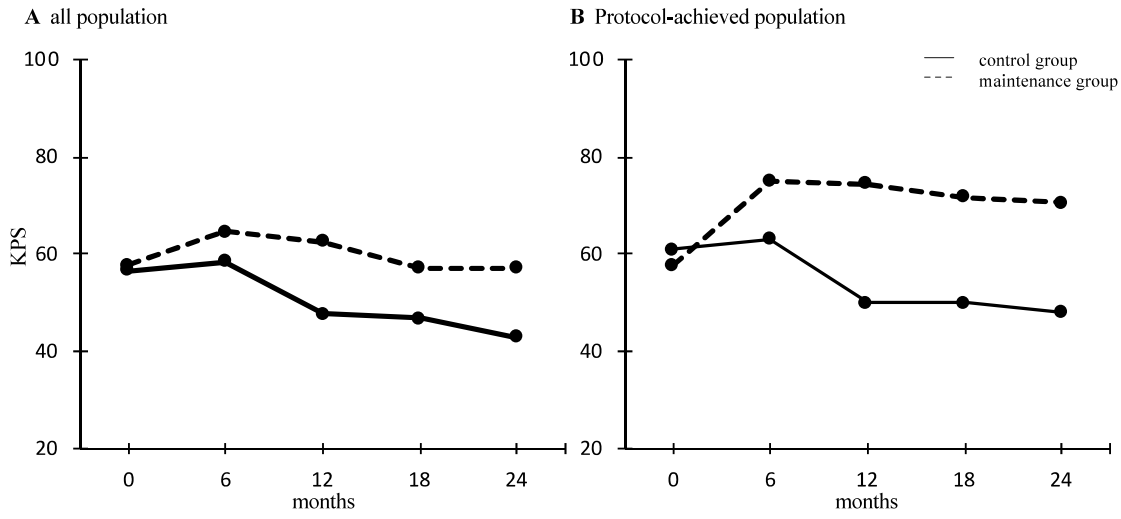

Figure 4. Mean KPS scores in the course of the 2-year follow-up period.
(A) All patients
(B) Protocol-achieved population
Solid line : control group; dashed line : maintenance group.

Table 3. Comparison of our study with previously reported findings

Reference	Regimen	No. of patients	1 year-PFS	2 year-PFS	3 year-PFS	1 year-OS	2 year-OS	3 year-OS
Nelson, 1992 (8)	WBRT	41	NA	NA	NA	48	28	NA
Thiel, 2010 (11)	MTX+IFOS+WBRT	154	NA	43.5	NA	NA	NA	NA
	MTX+IFOS	164	NA	30.7	NA	NA	NA	NA
Morris, 2013 (12)	MTX+R+PCZ+VCR+dose-reduced WBRT ITTgroup	52	65	57	51	85	81	77
	MTX+R+PCZ+VCR+dose-reduced WBRT per-protocol group	43	84	77	71	94	87	84
Ferreri, 2017 (14)	MTX+Ara-C±R±thiotepa+WBRT	55	NA	76	NA	NA	82	NA
	MTX+Ara-C±R±thiotepa+ASCT	58	NA	75	NA	NA	77	NA
Bromberg, 2019 (18)	MTX+BCNU+teniposide+prednisolone	100	58	NA	NA	79	65	61
	MTX+BCNU+teniposide+prednisolone+R	99	65	NA	NA	79	71	58
Current study	MTX+WBRT	18	22.9	15.2	15.2	77.8	72.2	33.1
	MTX±R, maintenance MTX	34	39.4	39.4	32.3	88.1	79	74.9

Abbreviations: WBRT, whole brain radiotherapy; MTX, methotrexate; IFOS, ifosfamide; R, rituximab; PCZ, procarbazine; VCR, vincristine; Ara-C, cytarabine; BCNU, carmustine; NA, not available

Based on these data, maintenance therapy might be appropriate for the elderly PCNSL patients with a poor KPS and low- or no tolerance for intensive chemotherapy or high-dose chemotherapy with ASCT. On the other hand, the PFS of our study was shorter than in earlier investigations. HD-MTX with or without rituximab might be insufficient as an induction chemotherapy in patients with newly diagnosed PCNSL. It is a further study on whether improvement of prognosis is obtained by introducing intensive chemotherapy for patients aged 70 and younger.

Although the efficacy of rituximab, a humanized anti-CD20 monoclonal antibody, against PCNSL is still incompletely understood, rituximab has been included in many PCNSL treatment protocols and shown to improve the CR rate and the duration of OS (18-20). In our study, no significance was found to add rituximab to induction therapy.

Methotrexate and WBRT can each cause cognitive dysfunction due to neurotoxicity, but there is synergistic toxicity when these modalities are combined. In PCNSL patients, the addition of WBRT to HD-MTX increases the risk of neurotoxicity due to leukoencephalopathy. Patients aged >60 years who received WBRT were significantly higher risk of delayed neurotoxicity and a reduction of KPS score (7, 10, 11). On the other hand, Chamberlain *et al*. (17) reported no cognitive decline was documented in surviving patients treated with HD-MTX maintenance therapy. Similarly in our study, KPS score tended to be maintained in patients achieving CR with HD-MTX maintenance therapy. However long-term effects of HD-MTX administration are not clear, longer neuropsychological follow-up is necessary to evaluate the relationship with neurotoxicity due to leukoencephalopathy.

This study has some limitations. The population in our retrospective, single center study was small and although both groups were similar with respect to their background, we used historical data to obtain a control group. This may have resulted in bias. Also, the patients in the maintenance group were not followed long enough to estimate their median survival at the time of analysis.

We report that induction therapy with HD-MTX with or without rituximab chemotherapy followed by continued monotherapy maintenance with HD-MTX improved the overall survival of patients with PCNSL. It was superior to chemoradiotherapy consisting of 3 cycles of HD-MTX followed by WBRT. Receiving maintenance therapy was an independent good prognostic indicator for the OS and the maintenance protocol avoided KPS deterioration.

CONFLICT OF INTEREST

We have no sources of financial support and no potential conflicts of interest.

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