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Primary central nervous system lymphoma: Retrospective analysis of 34 cases in a single centre

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Abstract

Objective: To retrospectively analyse outcomes in patients with primary central nervous system lymphoma (PCNSL), which is a malignant CNS non-Hodgkin's lymphoma with a poor prognosis.
Methods: This study retrospectively analysed the treatment and outcomes of patients with PCNSL, which were divided into two groups: surgery (S) group and surgery/biopsy+chemotherapy (SC) group. The latter group was further subdivided into four cohorts based on the treatment regimen: cyclophosphamide, epidoxorubicin, vincristine and prednisone (CHOP), high-dose methotrexate (HDM)+dexamethasone+rituximab (HDM+D+R), HDM+D+temozolomide (HDM+D+T), and HDM+D+R+T.
Results: The study enrolled 34 patients; 10 of which received surgery only. Between the S and SC groups, the median progression-free survival (PFS) and overall survival (OS) of intracranial PCNSLs ($n = 32$) were 8.5 months versus 29 months, respectively; and 8.5 months versus 54 months, respectively (5-year OS: 10.0% versus 48.7%, respectively; 2-year PFS: 0.0% versus 52.6%, respectively). Comparing the CHOP and HDM-based chemotherapy cohorts, the median PFS and OS were 15 months versus not achieved, respectively, and 25 months versus not achieved, respectively (5-year OS: 20.0% versus 60.8%, respectively; 2-year PFS: 20.0% versus 62.7%, respectively).

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Conclusion: Chemotherapy appears to provide a better OS and PFS for patients with PCNSLs compared with surgery alone. HDM+D+T and HDM+D+R+T may be effective choices for PCNSL treatment.

Keywords
Primary central nervous system lymphoma, chemotherapy, high-dose methotrexate, temozolomide

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare and malignant non-systemic CNS non-Hodgkin's lymphoma that is confined to the brain, eyes, leptomeninges, or spinal cord. It accounts for 3–4% of all CNS tumours and 4–6% of all extranodal lymphomas with a yearly incidence of 0–5 cases per 100 000 people.[1] According to the most recent World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissue, PCNSL should be limited in primary diffuse large B-cell lymphomas (DLBCL) in immunocompetent patients.[1] No effective treatment exists for PCNSL and its prognosis is unsatisfactory with a survival rate of less than 20–30% at 5 years and a median survival time of 10–20 months.[1] High-dose methotrexate (HDM)-based chemotherapy plays a central role in the management of PCNSL, and several novel therapeutic strategies have been developed, including HDM-based chemotherapy with CD20 antibody rituximab (R) or temozolomide (T) and stem cell transplantation therapy.[2–5] There has been no well-designed randomized trials to better define the optimal management of PCNSL. To investigate the efficacy of current treatment strategies and provide clinical evidence for effective standard treatment for PCNSL, the present study retrospectively analysed cases of PCNSL treated in our hospital and reviewed the available literature.

Patients and methods

Patient population

This retrospective study analysed clinical data from patients with newly diagnosed PCNSL who underwent surgical resection or a biopsy with pathological examination in the Department of Haematology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China between June 2009 and June 2016. Systemic examination, including magnetic resonance imaging (MRI) of the brain, lumbar puncture, bone marrow biopsy and cytology, chest and abdominal computed tomography and ophthalmological examination, confirmed that these lymphomas were confined to the brain or spinal cord, without other involvement or metastases. Patients treated prior to 2012 received either surgery alone or treatment with the cyclophosphamide, epidoxorubicin, vincristine and prednisone (CHOP) regimen or HDM-based regimen if the patient agreed to receive chemotherapy. All patients treated since 2012 received surgery/biopsy and HDM-based chemotherapy.

Written informed consent was obtained from all patients prior to being included in the study, and the study followed the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital,

Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China (approval registration no. 2017-534).

Treatment protocols

In the surgery only (S) group, patients received lymphoma resection only, without any chemotherapy treatment. In the surgery/biopsy+chemotherapy (SC) group, treatment consisted of four to six chemotherapy cycles, given at 3-week intervals. Intrathecal 50 mg cytarabine (Ara-C), 5 mg dexamethasone (D) and 15 mg methotrexate (M) were given once before each cycle. In the cohort that received CHOP, patients received 750 mg/m^2 cyclophosphamide on day 1, 75 mg/m^2 epidoxorubicin on day 1, 1.4 mg/m^2 (max 2 mg) vincristine on day 1, and 100 mg prednisone on days 1–5 for each cycle. In the cohort that received HDM+D+R, patients received 375 mg/m^2 rituximab on day 0 and 3 g/m^2 methotrexate on day 1 (24-h infusion on day 1 with folinic acid rescue) and 15 mg dexamethasone on days 1–5. In the cohort that received HDM+D+T, patients received 150 mg/m^2 temozolomide on days 1–5 for the first cycle and 200 mg/m^2 temozolomide on days 1–5 beginning with the second cycle, 3 g/m^2 methotrexate on day 1 (24-h infusion on day 1 with folinic acid rescue) and 15 mg dexamethasone on days 1–5. In the cohort that received MTX+D+R+T, patients received 375 mg/m^2 rituximab on day 0, 3 g/m^2 methotrexate on day 1 (24-h infusion on day 1 with folinic acid rescue), 150 mg/m^2 temozolomide on days 1–5 for the first cycle and 200 mg/m^2 temozolomide on days 1–5 beginning with the second cycle, and 15 mg dexamethasone on days 1–5.

Evaluation of efficacy and toxicity

Complete response (CR) rate, partial response (PR) rate, progression-free survival (PFS) and overall survival (OS) were analysed. Response was determined after four chemotherapy cycles by contrast-enhanced MRI of the brain using neuroradiographic response criteria.[6] PFS was calculated as the interval from treatment to relapse, progression or death or the date of last follow-up, while OS was calculated as the interval from treatment to death or the date of last follow-up. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events version 4.0.[7]

Statistical analyses

All statistical analyses were performed using Prism software version 7.0 (GraphPad Software, La Jolla, CA, USA). Differences in PFS and OS between the therapeutic groups and cohorts were analysed using the log-rank test. A two-sided P-value <0.05 was considered significant.

Results

A total of 34 patients (19 males; 15 females) with a median age of 56 years (range, 2 years 9 months to 76 years) were enrolled in the study. None of the cases of PCNSL was associated with immunodeficiency, transplantation, or HIV infection. There were two patients with PCNSL in the spinal cord and 32 patients with intracranial PCNSL. In the patients with intracranial PCNSL (18 males; 14 females), the median age was 55.5 years (range, 2 years 9 months to 76 years). There were 10 patients in the S group; and 22 patients in the SC group, including five patients in the CHOP cohort, six in the HDM+D+R cohort, eight in the HDM+D+T cohort and three in the HDM+R+D+T cohort. The two patients (one male; one female) with lesions in the spinal cord received surgery only. Details of the clinical and demographic characteristics, treatment regimens and prognosis of the patients with intracranial

Table 1. Clinical and demographic characteristics of patients ($n = 32$) with newly diagnosed intracranial primary central nervous system lymphoma (PCNSL) who underwent surgical resection alone or surgery/biopsy followed by chemotherapy.

Characteristic	Surgery group $n = 10$	Surgery/biopsy + chemotherapy group $n = 22$				Total cohort $n = 32$
		CHOP $n = 5$	HDM+D+R $n = 6$	HDM+D+T $n = 8$	HDM+D+R+T $n = 3$	
Age, years	63.5 (2.75–76)	55 (33–63)	52.5 (51–67)	49 (25–59)	57 (57–67)	55.5 (2.75–76)
Sex						
Male	6 (60.0)	3 (60.0)	4 (66.7)	4 (50.0)	1 (33.3)	18 (56.3)
Female	4 (40.0)	2 (40.0)	2 (33.3)	4 (50.0)	2 (66.7)	14 (43.8)
KPS at diagnosis, %	85 (60–90)	80 (60–90)	80 (60–90)	80 (30–90)	80 (70–90)	80 (30–90)
80–100	6 (60.0)	3 (60.0)	4 (66.7)	5 (62.5)	2 (66.7)	20 (62.5)
60–70	4 (40.0)	2 (40.0)	2 (33.3)	1 (12.5)	1 (33.3)	10 (31.3)
30–50	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)	2 (6.3)
Histologic type[8]						
DLBCL (non-GCB)	7 (70.0)	3 (60.0)	5 (83.3)	3 (37.5)	2(66.7)	20 (62.5)
DLBCL (GCB)	3 (30.0)	2 (40.0)	1 (16.7)	5 (62.5)	1(33.3)	12 (37.5)
Response to chemotherapy						
CR		1 (20.0)	3 (50.0)	4 (50.0)	2 (66.7)	10 (45.5)
PR		2 (40.0)	1 (16.7)	3 (37.5)	1 (33.3)	7 (31.8)
SD		0 (0.0)	1 (16.7)	1 (12.5)	0 (0.0)	2 (9.1)
PD		2 (40.0)	1 (16.7)	0 (0.0)	0 (0.0)	3 (13.6)
Treatment-related death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PFS, months	8.5 (0–24)	15 (1–29)	8 (7–29)	Not achieved (10–57)	Not achieved (12–25)	15 (0–57)
2-year PFS rate, %*	0.0	20.0	33.3	72.9	100.0	35.4
OS, months	8.5 (1–73)	25 (2–60)	15 (11–29)	Not achieved (15–68)	Not achieved (12–25)	30 (1–73)
5-year OS rate, %*	10.0	48.7 (20.0 in CHOP cohort; 60.8 in HDM-based chemotherapy cohorts)				34.9

Data presented as median (range) or *n* of patients (%).

CHOP, cyclophosphamide, epidoxorubicin, vincristine and prednisone; HDM, high-dose methotrexate; D, dexamethasone; R, rituximab; T, temozolomide; KPS, Karnofsky Performance Score; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell like; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival.

*Calculated by Prism software version 7.0 (GraphPad Software, La Jolla, CA, USA).

PCNSL are listed in Table 1.[8] The follow-up period ranged from 1 to 73 months.

In patients with intracranial PCNSLs ($n = 32$), the median PFS and OS of total PCNSLs in this current study were 15 months and 30 months, respectively, with a 5-year OS of 34.9% and a 2-year PFS of 35.4% (Figures 1a and 1b). In the S group, nine of 10 patients relapsed (90.0%). The CR and PR rates were 45.5% (10 of 22) and 31.8% (seven of 22) in the SC group; and 20.0% and 40.0%, 50.0% and 16.7%, 50.0% and 37.5%, and 66.7% and 33.3% for the CHOP, HDM+D+R, HDM+D+T and HDM+D+R+T cohorts, respectively (Table 1). Comparing the S and SC groups, the median PFS and median OS were 8.5 months versus

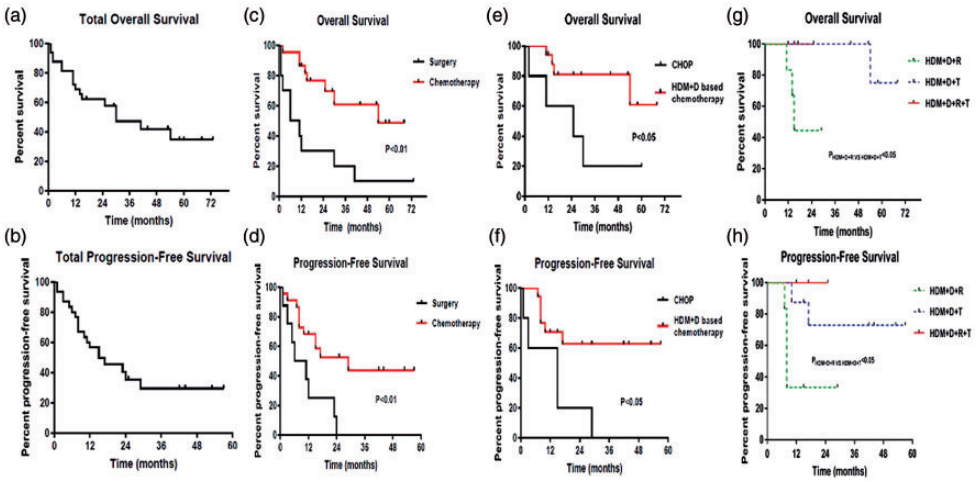

Figure 1. Overall survival (OS) and progression-free survival (PFS) curves for patients ($n = 32$) with newly diagnosed intracranial primary central nervous system lymphoma (PCNSL) who underwent surgical resection alone or surgery/biopsy followed by chemotherapy. (a) OS curve for total cohort of patients with intracranial PCNSL ($n = 32$; median OS, 30 months; 5-year OS, 34.9%). (b) PFS curve for total cohort of patients with intracranial PCNSL ($n = 32$; median PFS, 15 months; 2-year PFS, 35.4%). (c) OS curves for the surgery (black; $n = 10$; median OS, 8.5 months; 5-year OS, 10.0%) and chemotherapy groups (red; $n = 22$; median OS, 54 months; 5-year OS, 48.7%; $P < 0.01$ versus surgery group). (d) PFS curves for the surgery (black; $n = 10$; median PFS, 8.5 months; 2-year PFS, 0.0%) and chemotherapy groups (red; $n = 22$; median PFS, 29 months; 2-year PFS: 52.6%; $P < 0.01$ versus surgery group). (e) OS curves for the cyclophosphamide, epidoxorubicin, vincristine and prednisone (CHOP; black; $n = 5$; median OS, 25 months; 5-year OS, 20.0%) and high-dose methotrexate (HDM)-based chemotherapy cohorts (red; $n = 17$; median OS, not achieved; 5-year OS, 60.8%; $P < 0.05$ versus the CHOP cohort). (f) PFS curves for the CHOP (black; $n = 5$; median PFS, 15 months; 2-year PFS, 20.0%) and HDM-based chemotherapy cohort (red; $n = 17$; median PFS, not achieved; 2-year PFS, 62.7%; $P < 0.05$ versus the CHOP cohort). (g) OS curves for the HDM-based chemotherapy cohorts, HDM+D+R cohort (green; $n = 6$; median OS, 15 months; 2-year OS, 44.4%), HDM+D+T cohort (blue; $n = 8$; median OS, not achieved; 2-year OS, 100.0%), and HDM+D+R+T cohort (red; $n = 3$; median OS, not achieved;2-year OS, 100.0%) ($P < 0.05$ for HDM+D+R cohort versus HDM+D+T cohort only). (h) PFS curves for the HDM-based chemotherapy cohorts, HDM+D+R cohort (green; $n = 6$; median PFS, 8 months; 2-year PFS, 33.3%), HDM+D+T cohort (blue; $n = 8$; median PFS, not achieved; 2-year PFS, 72.9%), and HDM+D+R+T cohort (red; $n = 3$; median PFS, not achieved; 2-year PFS, 100.0%) ($P < 0.05$ for HDM+D+R cohort versus HDM+D+T cohort only). Differences in PFS and OS between the therapeutic groups and cohorts were analysed using the log-rank test. D, dexamethasone; R, rituximab; T, temozolomide. The colour version of this figure is available at: http://imr.sagepub.com.

29 months, respectively ($P < 0.01$), and 8.5 months versus 54 months, respectively ($P < 0.01$); 5-year OS was 10.0% versus 48.7%, respectively ($P < 0.01$); and 2-year PFS was 0.0% versus 52.6%, respectively ($P < 0.01$) (Figures 1c and 1d). Comparing the CHOP and HDM-based chemotherapy cohorts, the median PFS and OS were 15 months versus not achieved, respectively ($P < 0.05$), and 25 months versus not achieved, respectively ($P < 0.05$); 5-year OS was 20.0% versus 60.8%, respectively ($P < 0.05$); and 2-year PFS was 20.0% versus 62.7%, respectively ($P < 0.05$) (Figures 1e and 1f). In HDM-based chemotherapy, the median PFS and OS of the HDM+D+R cohort were 8 months and 15 months, respectively; for the HDM+D+T and HDM+D+R+T cohorts, both median PFS and OS were not achieved ($P < 0.05$ for HDM+D+R cohort versus HDM+D+T cohort) (Figures 1g and 1h). The study also compared the PFS and OS between the S group and each chemotherapy regimen cohort (Figures 2a and 2b). Two patients with lesions in the spinal cord received surgery only; one was still alive at 80 months, and the other survived for 52 months.

The clinical and laboratory toxicities that were observed in the SC group are listed in Table 2. A total of 21 cycles (mean, 4.2 cycles per patient; range, 1–6 cycles of therapy), 34 cycles (mean, 5.7 cycles per patient; range, 4–6 cycles of therapy), 42 cycles (mean, 5.3 cycles per patient; range, 4–6 cycles of therapy), and 18 cycles (mean, 6.0 cycles per patient; range, 6 cycles of therapy)

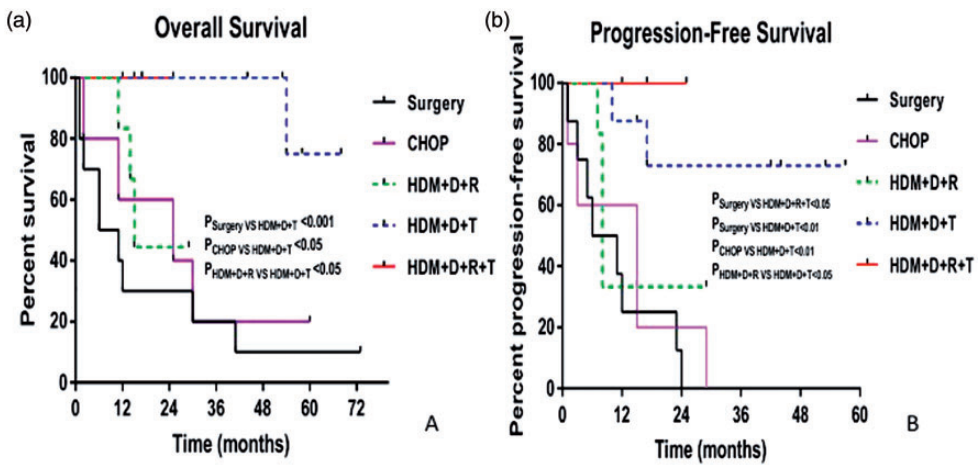

Figure 2. Overall survival (OS) and progression-free survival (PFS) curves for patients ($n = 32$) with newly diagnosed intracranial primary central nervous system lymphoma (PCNSL) who underwent surgical resection alone or surgery/biopsy followed by chemotherapy. (a) OS curve for patients in the surgery group and chemotherapy cohorts. There were significant differences between the surgery group and the HDM+D+T cohort ($P < 0.001$), between the CHOP and HDM+D+T cohorts ($P < 0.05$), and between the HDM+D+R and HDM+D+T cohorts ($P < 0.05$). (b) PFS curves for patients in the surgery group and chemotherapy cohorts. There were significant differences between the surgery group and the HDM+D+T cohort ($P < 0.01$), between the surgery group and the HDM+D+R+T cohort ($P < 0.05$), between the CHOP and HDM+D+T cohorts ($P < 0.01$), and between the HDM+D+R and HDM+D+T cohorts ($P < 0.05$). Differences in PFS and OS between the therapeutic groups and cohorts were analysed using the log-rank test. HDM, high-dose methotrexate; D, dexamethasone; T, temozolomide; CHOP, cyclophosphamide, epidoxorubicin, vincristine and prednisone; R, rituximab. The colour version of this figure is available at: http://imr.sagepub.com.

Table 2. Toxicity experienced by patients ($n = 22$) with newly diagnosed intracranial primary central nervous system lymphoma (PCNSL) who underwent surgery/biopsy followed by one of four chemotherapy regimens.

	Surgery/biopsy + chemotherapy group $n = 22$			
Adverse event	CHOP $n = 5$	HDM+D+R $n = 6$	HDM+D+T $n = 8$	HDM+D+R+T $n = 3$
Total cycles/patients	21/5	34/6	42/8	18/3
Clinical toxicities				
Fatigue				
Grade 1–2	15 (71.4)	25 (73.5)	28 (66.7)	15 (83.3)
Grade 3–4	2 (9.5)	1 (2.9)	3 (7.1)	3 (16.7)
Nausea				
Grade 1–2	10 (47.6)	21 (61.8)	24 (57.1)	8 (44.4)
Grade 3–4	0 (0.0)	3 (8.8)	4 (9.5)	1 (5.6)
Vomiting				
Grade 1–2	5 (23.8)	8 (23.5)	10 (23.8)	5 (27.8)
Grade 3–4	0 (0.0)	1 (2.9)	2 (4.8)	0 (0.0)
Mucositis				
Grade 1–2	4 (19.0)	10 (29.4)	12 (28.6)	5 (27.8)
Grade 3–4	0 (0.0)	2 (5.9)	2 (4.8)	1 (5.6)
Laboratory toxicities				
Haematological				
Haemoglobin				
Grade 1–2	13 (61.9)	18 (52.9)	20 (47.6)	10 (55.6)
Grade 3–4	1 (4.8)	2 (5.9)	1 (2.4)	1 (5.6)
Leukocytes				
Grade 1–2	15 (71.4)	26 (76.5)	32 (76.2)	13 (72.2)
Grade 3–4	6 (28.6)	6 (17.6)	8 (19.0)	4 (22.2)
Neutrophils				
Grade 1–2	15 (71.4)	20 (58.8)	25 (59.5)	12 (66.7)
Grade 3–4	3 (14.3)	4 (11.8)	5 (11.9)	3 (16.7)
Platelets				
Grade 1–2	14 (66.7)	20 (58.8)	22 (52.4)	10 (55.6)
Grade 3–4	0 (0.0)	2 (5.9)	3 (7.1)	1 (5.6)
Hepatic				
Transaminases				
Grade 1–2	4 (19.0)	8 (23.5)	11 (26.2)	5 (27.8)
Grade 3–4	1 (4.8)	1 (2.9)	0 (0.0)	0 (0.0)
Bilirubin				
Grade 1–2	2 (9.5)	5 (14.7)	5 (11.9)	2 (11.1)
Grade 3–4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data presented as *n* of chemotherapy cycles (%).

CHOP, cyclophosphamide, epidoxorubicin, vincristine and prednisone; HDM, high-dose methotrexate; D, dexamethasone; R, rituximab; T, temozolomide.

of chemotherapy were administered in the CHOP, HDM+D+R, HDM+D+T and HDM+D+R+T cohorts, respectively. The major toxicities were haematological: grade 3 or 4 neutropenia appeared in 3 cycles (14.3%), 4 cycles (11.8%), 5 cycles (11.9%) and 3 cycles (16.7%) in the CHOP, HDM+D+R, HDM+D+T and HDM+D+R+T cohorts, respectively. Hepatic toxicities and mucositis were minor, and there were no treatment-related deaths.

Discussion

Primary central nervous system lymphomas are aggressive tumours, so prompt diagnosis and effective treatment are necessary to improve the chances of achieving remission and survival. Diagnosis is usually difficult before biopsy, because the symptoms and general imaging examination of PCNSL are not specific. Thus, the majority of cases are identified by cerebral biopsy. MRI characteristics show diagnostic promise. For example, PCNSLs usually present on MRI as unique or multiple lesions, appearing as isointense or hypointense on T1-weighted images, isointense or hyperintense on T2-weighted images, homogeneously enhanced on contrast-enhanced T1-weighted images, hyperintense on fast fluid attenuated inversion recovery images and hyperintense on diffusion-weighted imaging.[9] PCNSLs can show different patterns of enhancement, such as ring-like, open-ring-shaped with a 'notch sign' and a butterfly-shaped structure, which is a typical imaging manifestation for PCNSLs in the corpus callosum.[9,10] The apparent diffusion coefficient of malignant lymphomas are lower than those of gliomas.[11] The sensitivity and specificity for discriminating between malignant lymphomas and gliomas are reported to be 80%–90%,[11] but some research showed the difference was not statistically significant.[12] Large lipid peaks on single-voxel proton MR spectroscopy (^{1}H-MRS) is also characteristic of malignant PCNSLs. For example, a previous study compared ^{1}H-MRS of patients with malignant PCNSLs and gliomas, and found that large lipid peaks were observed in all patients with malignant PCNSLs and parts of malignant gliomas.[13] In homogeneously enhanced tumours, including 15 cases of malignant PCNSLs and seven cases of gliomas, large lipid peaks were observed in all patients with malignant PCNSLs, but small or absent in gliomas.[13]

The treatment of PCNSLs is in a process of development and refinement. The role of surgery is limited for most malignant CNS tumours, being used mainly for diagnosis and intracranial decompression. Because conventional chemotherapy drugs cannot cross the blood–brain barrier (BBB), whole-brain radiotherapy (WBRT) is a more effective treatment method. However, survival after WBRT does not usually exceed 12–18 months, and there is a high risk of delayed neurotoxic effects.[14] The best treatment strategy remains controversial and WBRT is only advisable for patients with progressive or residual disease after chemotherapy.[14] Chemotherapy that crosses the BBB has demonstrated an improved response in PCNSLs.[14] In this current study, survival in the SC group (median PFS, 29 months; median OS, 54 months; 2-year PFS, 52.6%; 5-year OS, 48.7%) was significantly better than the S group. The 5-year OS in the CHOP cohort was only 20.0%, which may be because CHOP is not able to cross the BBB. Therefore, CHOP regimens and derivatives are not recommended for the treatment of PCNSLs.[14]

High-dose methotrexate-based chemotherapy has become a first-line treatment of PCNSLs. Methotrexate should be given at doses of at least $3g/m^2$ so as to cross the BBB and yield cytotoxic levels in the cerebrospinalfluid.[12] It has been demonstrated that combining HDM and other

chemotherapeutic agents improves responses compared with HDM alone. For example, a randomized study comparing HDM alone with HDM plus high-dose Ara-C showed a statistically significant improvement with the combination, which is now considered current standard therapy.[15]

There has been a growing trend to combine HDM with new chemotherapy agents and examine any possible changes in efficacy. Rituximab is a chimeric monoclonal antibody against the CD20 antigen on B lymphocytes. It has successfully improved outcome in patients with systemic DLBCL and has become a standard component of treatment for DLBCL.[16,17] However, the impact of rituximab in PCNSLs is less clear. A retrospective study comparing HDM alone with HDM plus rituximab for newly diagnosed PCNSLs reported a CR rate of 73% in 27 patients treated with HDM plus rituximab compared with 36% in 54 patients treated with HDM alone.[18] The median PFS was 26.7 months in the HDM plus rituximab cohort compared with 4.5 months in the HDM cohort.[18] Another study reported a CR rate of 91% and a PFS of 22 months after administration of the HDM plus rituximab regimen.[19] These studies suggest that the addition of rituximab to HDM-based regimens improves outcomes in PCNSL patients.[18,19] However, other studies have reported different findings. For example, a previous study compared two subgroups of patients treated with HDM or HDM+R and found the 5-year PFS rate was 17% and the OS rate was 38% with no difference between the two groups.[20] They concluded that rituximab may not be effective in patients with very aggressive PCNSLs, and only those with less aggressive cancers may derive some benefit.[20] In this current study, the CR rate was 50.0% in the six patients in the HDM+D+R cohort, with a median PFS of 8 months (range, 7–29 months) and a median OS of 15 months (range, 11–29 months), with a 2-year PFS of 33.3% and a 2-year OS of 44.4%. Large prospective randomized trials are needed to determine the true potential of this combination therapy.

Temozolomide is a novel alkylating agent with good BBB penetration and low toxicity, which is widely used for treating high-grade gliomas. It was first considered as a salvage therapy for PCNSLs and is beneficial for relapsing PCNSLs.[21] A previous study used temozolomide alone as first-line therapy for two older patients with PCNSL and achieved CR.[22] Later, first-line chemotherapy with temozolomide showed good tolerability and some activity in elderly patients with PCNSL (CR rate, 47%; median PFS, 5 months; median OS, 21 months) in a larger study.[23] Survival with a combination of HDM and temozolomide was better than HDM combined with other chemotherapy agents (CR rate, 55%; median PFS, 8 months; median OS, 35 months).[24] However, the efficacy of temozolomide therapy does not seem consistent and it may be influenced by many factors, such as the *MGMT* gene promoter status.[23] A previous study, which analysed 40 patients with PCNSL (median age, 52 years; range, 20–65 years) who received an innovative regimen combining cytarabine and methotrexate with temozolomide without radiotherapy or intrathecal chemotherapy, reported a CR rate of 85% and a median OS of 63.9 months; and grade II nephrotoxicty was observed in two patients and grade III and IV haematotoxicity was observed in five patients.[25] Another study reported on 41 patients with newly diagnosed PCNSL who were treated with methotrexate and temozolomide (M+T) or methotrexate and Ara-C (M+C).[4] The objective response rate, CR rate, 5-year PFS and OS of the M+T group were comparable with those of the M+C group; and grade 3–4 haematological toxicities were

more common in the M+C group than in the M+T group.[4] The CR rate in the HDM+D+T cohort in the current study was 50.0%, the median PFS and OS were both not achieved, the 2-year PFS was 72.9% and the 2-year OS was 100%. All of these studies suggest that the regimens of methotrexate with/without Ara-C combined with temozolomide provide an effective therapy with an acceptable toxicity profile for PCNSLs.

There have been no studies comparing the HDM+D+R and the HDM+D+T regimens in patients with PCNSL. The current study showed that the PFS and OS of HDM+D+T were significantly better than HDM+D+R ($P < 0.05$). This difference may be related to the BBB permeability of temozolomide and rituximab. Temozolomide has good BBB penetration, while the BBB penetration by rituximab is not as strong due to its high molecular weight.[24,26] In this current study, three patients received treatment with the HDM+D+R+T regimen. Both the median PFS and OS were not achieved and there was acceptable toxicity. Two patients achieved CR and the third patient achieved PR after four cycles. None of the three patients has relapsed. These findings suggest that the HDM+D+R+T regimen could be a good choice for treating PCNSLs, but efficacy and safety should be further examined and validated by future larger randomized trials.

There were two patients with PCNSL in the spinal cord and both received only surgical treatment. One had an OS of 52 months, while the other was still alive at 80 months. It seems as if the location of the primary lymphoma, either in the spine or brain, affects survival and response to treatment. PCNSL located in the spinal cord treated with surgery alone appears to be associated with a good prognosis. A review of the clinicopathological characteristics and prognostic factors for primary spinal epidural lymphoma found an association with a relatively good prognosis.[27] The disease-free survival for patients receiving surgery alone was 23.3%, which was lower than the other treatment groups, but the OS rate was 80% and there were no significant differences between treatment regimens.[27]

In conclusion, this current study compared the outcomes of patients with newly diagnosed PCNSLs after different treatment regimens. Based on these findings, we would recommend HDM-based chemotherapy as first-line treatment for PCNSLs. The HDM+D+T or HDM+D+R+T regimens may provide an even better prognosis. This study was limited by its retrospective nature and small sample size, so these conclusions should be verified and built upon by more clinical trials with more patients. Further studies are also needed to refine the PCNSL treatment strategies currently in use or being studied.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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