Characteristics and Outcomes of Primary Central Nervous System Lymphoma: A Retrospective Study of 91 Cases in a Chinese Population

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■ BACKGROUND: **Primary central nervous system lymphoma (PCNSL) is a rare disease affecting the brain, leptomeninges, spinal cord, cerebrospinal fluid, or vitreoretinal compartment, without evidence of systemic disease. Prognosis is still poor after intensive methotrexate-based chemotherapy.**

■ METHODS: **Clinical data of 91 patients treated in a tertiary referral center during a 13-year period were retrospectively reviewed.**

■ RESULTS: **The estimated median progression-free survival and overall survival (OS) for the entire cohort were 39.1 months (95% confidence interval [CI], 14.1–64.0 months) and 54.5 months (95% CI, 28.9–80.1 months), respectively. Estimated 5-year progression-free survival and OS were 37.0% ± 6.5% and 47.5% ± 7.5%. Survival was associated with cycles of methotrexate only in multivariate analysis. Seventy-four patients received methotrexate-based chemotherapy after diagnosis. Thirty-nine patients experienced disease progression. Patients with relapsed/refractory disease had a poor survival, with median second OS (calculated from the date of first disease progression to the time of death from any cause) being 7.2 months (95% CI, 2.5–12.00 months). Three patients responded to ibrutinib after disease progression and incurred no fungal infection.**

■ CONCLUSIONS: **The outcomes of patients with PCNSL treated in our cohort are still poor. Relapse or refractory PCNSL and those not tolerating aggressive chemotherapy urgently require new approaches to improve their still dismal prognosis. Novel agents such as ibrutinib have shown promising clinical activity. Future studies should focus on the predictive biomarkers for the treatment of PCNSL with novel agents to provide precision medicine for PCNSL.**

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an unusual form of aggressive non-Hodgkin lymphoma affecting the brain, leptomeninges, spinal cord, cerebrospinal fluid (CSF), or vitreoretinal compartment, without evidence of systemic disease.[1] The overall incidence of PCNSL is rare, accounting for <3% of all cases of non-Hodgkin lymphoma and 3% of all primary central nervous system tumors.[2] Approximately 95% of PCNSL cases present as large B-cell lymphomas and 5% have other histologies including T-cell, Burkitt, lymphoblastic, and marginal zone lymphomas.[3]

PCNSL is usually diagnosed by stereotactic brain biopsy and subsequent neuropathologic workup. In contrast to treatment of other brain tumors, resection is generally discouraged, and main treatment strategies comprise different chemotherapy and radiotherapy protocols. However, treatment of PCNSL is complicated by the presence of the blood-brain barrier (BBB), which renders most systemic lymphoma therapies ineffective.[4] High-dose (HD) methotrexate (MTX), one of the few agents capable of penetrating

Key words
- Chemotherapy
- Craniotomy
- Primary central nervous system lymphoma
- Radiotherapy

Abbreviations and Acronyms
BBB: Blood-brain barrier
CI: Confidence interval
CSF: Cerebrospinal fluid
HD: High-dose
IV: Intravenous
LDH: Lactose dehydrogenase
MTX: Methotrexate
OS: Overall survival
PCNSL: Primary central nervous system lymphoma
PFS: Progression-free survival
PR: Partial remission
PS: Performance status
SD: Stable disease
WBRT: Whole-brain radiotherapy

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Citation: World Neurosurg. (2019) 123:e15-e24.
https://doi.org/10.1016/j.wneu.2018.10.034

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

1878-8750/$ - see front matter

the BBB, is commonly used as a first-line treatment for PCNSL. When paired with other agents such as HD cytarabine, temozolomide, and rituximab, HD-MTX combination therapy offers superior prognosis compared with single therapeutics alone.[5-11] Although combination therapy is effective for many patients, 20%–30% of patients with PCNSL relapse within 6 months, even after intensive MTX induction treatment,[11] highlighting the importance of consolidation therapy. Consolidation therapy for PCNSL typically consists of whole-brain radiotherapy (WBRT), autologous stem cell transplantation, and oral drugs.[12]

Because of its rarity, there are no standard treatment protocols for PCNSL. In this retrospective study, we retrospectively reviewed 91 cases of pathology-confirmed PCNSL during a 13-year period (2004–2017) in a tertiary referral institute in China to evaluate the characteristics and outcome. The situation in China might be different from that in developed countries. Many effective drugs are unavailable in China and many patients could not afford the cost for treatment. It might be difficult for doctors to work out a treatment protocol. Our study could offer an overview of the treatment for PCNSL in China.

METHODS

Patients

Patients with newly diagnosed PCNSL in Guangdong General Hospital, Guangzhou, Guangdong, China, between May 2004 and November 2017 were retrospectively analyzed. The inclusion criteria of this study were PCNSL diagnosis confirmed by pathologic examination, without any evidence of lymphoma outside the brain, meninges, eyes, spinal cord, or nerve roots detected by bone marrow biopsy, computed tomography, or positron emission tomography computed tomography. Exclusion criteria included any other central nervous system disease, including other tumors, hereditary disease, or metabolic disease. All patients in this cohort were serum negative for human immunodeficiency virus because those who were serum positive before surgery were transferred to a specialized hospital. The trial was approved by the ethical institutional review board of the Guangdong General Hospital in accordance with the Declaration of Helsinki, and all patients gave written informed consent.

Chemotherapy and Radiotherapy

Chemotherapy and radiotherapy were given as follows. During the induction phase, MTX 3.5 g/m^2 was administered intravenously (IV) for 3 hours every 14 days for 6–8 cycles. Before administration, urine was alkalinized with IV sodium bicarbonate. Each dose was followed 12 hours later by leucovorin 15 mg IV every 6 hours. MTX levels were measured daily. Leucovorin was stopped when the MTX levels decreased <10 mmol/L. Before January 2013, cytarabine 2 g/m^2 (1 hour infusion, twice daily, every 12 hours) on days 2 and 3 was added to HD-MTX. After January 2013, temozolomide 150 mg/m^2 was administered for 5 days after MTX levels decreased <10 mmol/L on cycles 2, 4, 6, and 8. Both before and after January 2013, patients deemed too frail for combination therapy received only HD-MTX. Rituximab 375 mg/m^2 was administered in those patients who could afford the cost the day before the initial MTX treatment. Optional WBRT 36 Gy was administered for consolidation before January 2013. Twelve cycles of temozolomide 150 mg/m^2 for 5 days, with each cycle lasting 28 days, was given after radiologic complete remission after January 2013. Active clinical monitoring was administered to those who were reluctant to receive consolidation or maintenance therapy. For patients showing only a radiologic partial remission (PR), WBRT 36 Gy was used as the treatment of choice for consolidation therapy. For those with progressive disease, salvage chemotherapy, WBRT, or other drugs were given at the discretion of the patient and the attending physician.

Evaluation of Response and Follow-Up

The patient response was determined after every 2 courses of induction chemotherapy by contrast-enhanced magnetic resonance imaging of the brain. Radiographic responses were graded as complete remission, PR (>50% decrease in enhancing tumor), progressive disease (>25% increase in a lesion; progressive or newly emergent meningeal or ocular disease), or stable disease. Overall response rate was defined as the percentage of patients with complete remission or PR. After completion of therapy, patients were followed up every 3 months for 5 years clinically and radiologic examinations were performed in those who had symptoms.

Evaluation of Toxicity

Treatment toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 4.0.

Statistics

Overall survival (OS) was calculated from the date of diagnosis to the time of death from any cause. Progression-free survival (PFS) was calculated from the start of treatment to the time of disease progression or death as a result of PCNSL. The Kaplan-Meier method was used to calculate all survival end points, and survival was compared between groups using the log-rank test. Multivariate Cox proportional hazards regression analysis was performed for multivariate analysis. Variables with $P < 0.05$ were considered statistically significant in the final models. χ^2 analysis was used to compare the distribution of factors between groups, with the Wilcoxon 2-sample test applied for continuous variables. All statistical analyses were performed using SPSS software (version 22.0 [IBM Corp., Armonk, New York, USA]).

RESULTS

Baseline Characteristics

During a 13-year period in Guangdong General Hospital, China, 91 patients with PCNSL were identified. Baseline characteristics are shown in **Table 1**. Forty-eight patients (52.75%) were male, and the male/female ratio was 1.12. The median age of patients was 55 years (range, 18–78 years). The Eastern Cooperative Oncology Group performance status (PS) of patients was 1 or 2 in 64.84% and 3 or 4 in 35.16% at the time of diagnosis. Twelve patients (13.19%) had increased lactose dehydrogenase (LDH) levels. Fifty-four patients (59.34%) had multiple lesions. More than half of the observed lesions (53/91, 58.24%) occurred in the deep region, defined as the periventricular tissue, basal ganglia, corpus callosum, brainstem, and/or cerebellum. Thirty-one patients received

Table 1. Baseline Characteristics

Characteristics	N (%)
Median age, years (range)	55 (18–78)
Age (years)	
≤60	66 (72.53)
>60	25 (27.47)
Sex	
Male	48 (52.75)
Female	43 (47.25)
Performance status	
≤2	59 (64.84)
>2	32 (35.16)
Histology	
DLBCL-non-GCB	58 (63.74)
DLBCL-GCB	24 (26.37)
DLBCL-NOS	8 (8.79)
Natural killer/T-cell lymphoma	1 (1.10)
Deep brain lesions	
Present	53 (58.24)
Absent	38 (41.76)
Number of lesions	
1	37 (40.66)
≥2	54 (59.34)
Cerebrospinal fluid protein	
Normal	8 (8.79)
Increased	23 (25.27)
NA	60 (65.93)
Lactate dehydrogenase	
Normal	71 (78.02)
Increased	12 (13.19)
NA	8 (8.79)
Radiotherapy	
Yes	29 (31.86)
No	62 (68.13)
Rituximab	
Yes	40 (43.95)
No	51 (56.04)
High-dose methotrexate ≥4 cycles	
Yes	61 (67.03)
No	30 (32.96)
Ocular involvement	
Present	3 (3.30)
Absent	88 (96.70)

NA, not applicable; DLBCL, diffuse large B cell lymphoma; GCB, germinal central B-cell like; NOS, non-special type.

CSF analysis before surgery. However, lymphoma cells were not found in the CSF and thus all received biopsy.

Factors Affecting Survival

The median follow-up time for eligible living patients was 18.9 months (range, 0.5–135.2 months). Three patients received only 1 cycle of HD-MTX-based chemotherapy and stopped treatment for economic reasons. Nine patients refused further treatment after diagnosis for economic reasons. These 12 patients were lost to follow-up. Five patients died of intracranial infection before the initiation of chemotherapy. The remaining 74 patients received HD-MTX-based chemotherapy. As shown in **Figure 1**, the estimated median PFS and OS for the entire cohort was 39.1 months (95% confidence interval [CI], 14.1–64.0 months) and 54.5 months (95% CI, 28.9–80.1 months), respectively. The estimated 5-year PFS and OS were 37.0% ± 6.5% and 47.5% ± 7.5%.

Clinical parameters were subjected to univariate analyses to evaluate their impact on PFS and OS. As shown in **Table 2**, PFS and OS were better for those who received rituximab and >4 cycles of HD-MTX chemotherapy (PFS, $P = 0.01$, $P = 0.00$; OS, $P = 0.02$, $P = 0.00$). Age, sex, PS >2, histology, deep brain lesion, number of lesions, increased levels of cerebrospinal protein, increased levels of LDH, and use of radiotherapy were not associated with PFS and OS in univariate analyses.

To further assess independent prognostic factors, multivariate analyses were performed using the Cox proportional hazards model including age, sex, PS >2, histology, deep brain lesion, number of lesions, use of radiotherapy, use of rituximab, and use of >4 cycles of HD-MTX chemotherapy. In multivariate analyses, only use of >4 cycles of HD-MTX chemotherapy was an independent prognostic factor for OS and PFS ($P = 0.00$, $P = 0.00$) (**Table 3**).

Diagnostic Methods and Survival Outcome

Patients were diagnosed with PCNSL via craniotomy or stereotactic biopsy. In patients with a single lesion, the tumor was totally removed in 13, partially removed in 13, and biopsied in 13 ones. Twenty-one patients with multiple lesions received partial resection of tumor and the other 33 received stereotactic biopsy. Three patients died of intracranial infection after craniotomy and 1 after stereotactic biopsy.

Thirty-two patients with a single lesion received HD-MTX-based chemotherapy after diagnosis. In this cohort, there was no significant difference considering OS between patients who received total resection of tumor, partial resection of tumor, and stereotactic biopsy (total resection vs. partial resection, $P = 0.85$; total resection vs. stereotactic biopsy, $P = 0.80$; partial resection vs. stereotactic biopsy: $P = 0.83$; **Table 4**). Patients with partial resection of tumor had a significantly shorter PFS. However, no significant difference was observed between patients with total resection and stereotactic biopsy (total resection vs. partial resection, $P = 0.14$; total resection vs. stereotactic biopsy, $P = 0.65$; partial resection vs. stereotactic biopsy: $P = 0.03$; **Table 4**).

Forty-two patients with multiple lesions received HD-MTX-based chemotherapy. In this cohort, there was no significant difference considering OS and PFS between patients who received partial resection of tumor and stereotactic biopsy (**Table 4**).

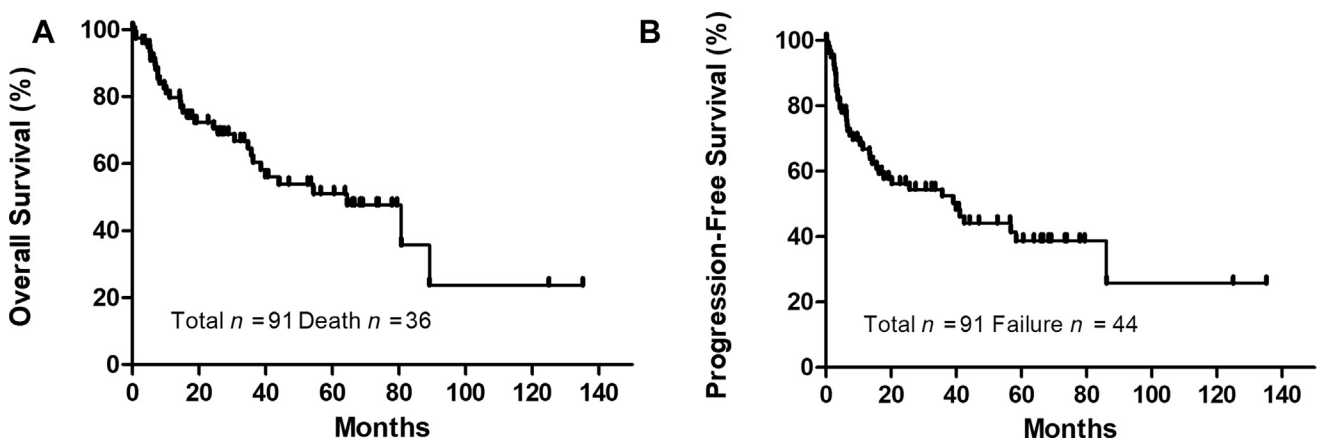


Figure 1. Survival of patients with primary central nervous system lymphoma. (**A**) Overall survival. (**B**) Progression-free survival.

Chemotherapy and Radiotherapy

Treatment after diagnosis is important for survival in patients with PCNSL. To further assess the impact of different regimens on survival, the outcome of patients with different treatments was compared.

After pathologic confirmation of PCNSL, 74 patients received >2 cycles of chemotherapy. As shown in Table 5, patients who received both HD-MTX and cytarabine had the longest PFS and OS. However, all patients treated with cytarabine developed grade 3 or 4 toxicity, whereas only 5 patients treated with HD-MTX with or without rituximab (5/13, 38.5%) and 3 patients treated with temozolomide (3/40, 7.5%) had grade 3 or 4 toxicity. Use of rituximab was associated with longer PFS and OS in patients treated with HD-MTX and temozolomide.

Fifty-four patients showed a response to HD-MTX-based chemotherapy. In this group of patients, 15 received WBRT, 21 received temozolomide maintenance, and 18 received active monitoring after induction chemotherapy. As shown in Table 6, no significant difference considering PFS and OS was found among the 3 groups.

Survival of Patients with Relapsed/Refractory PCNSL

Thirty-nine patients showed disease progression after or during first-line treatment; characteristics at first disease progression are listed in Table 7. More than half of relapse/refractory patients had disease progression in the first year after first-line treatment. These patients were treated with numerous lines of therapy as shown in Table 7. For patients who relapsed after the completion of first-line treatment, HD-MTX-based chemotherapy was used again. Two patients showed relapse outside the central nervous system and were treated with systemic lymphoma drugs.

Ibrutinib was used in 3 patients and had a response rate of 100%. One patient showed disease progression after receiving 4 cycles of HD-MTX plus temozolomide and showed no response to the subsequent lenalidomide single-agent treatment. He then received single ibrutinib 560 mg daily and had PR. However, he died of PCNSL progression after 3 months of ibrutinib. Another patient showed disease progression after receiving 2 cycles of HD-MTX plus temozolomide and then received 6 cycles of isofomide plus etoposide. He showed disease progression after stem cells were harvested. He received radiotherapy and lenalidomide maintenance thereafter. He relapsed again 6 months later and ibrutinib 560 mg daily was given. He received ibrutinib for 1 months and his symptoms improved. The third patient relapsed 1 year later after receiving 8 cycles of HD-MTX. He then received 2 cycles of HD-MTX plus rituximab and cytarabine. However, he could not tolerate the side effects. He then received 6 cycles of HD-MTX plus rituximab and ibrutinib and ibrutinib maintenance. He received 560 mg ibrutinib for 8 months and was in good condition. No *Aspergillus* infection was seen in these 3 patients.

Patients with relapsed/refractory disease had a poor survival, with median second OS (calculated from the date of first disease progression to the time of death from any cause) of 7.2 months (95% CI, 2.5–12.00 months).

DISCUSSION

Because of the rarity of PCNSL, there is no standard treatment protocol. Controversy exists regarding diagnostic procedure (biopsy or craniotomy), treatment strategies, and prognostic factors.

Role of Craniotomy in PCNSL

The first controversial issue is the value of craniotomy in PCNSL. In contrast to management of other intra-axial tumors, including brain metastasis and diffusely infiltrative gliomas, surgery for cytoreduction is generally not recommended in PCNSL.[13-15] The exclusion of cytoreductive surgery from first-line management of PCNSL is largely caused by results from studies concluding that resection offered no benefit and potentially worsened outcome.[13-15] In our cohort, cytoreductive surgery was also not associated with better survival. Moreover, 3 patients (3/48, 6.25%) died of intracranial infection during craniotomy. However, our study has a limitation. Most of the craniotomies, such as gross total resections, were performed 5 years ago. At that time, some

Table 2. Univariate Analysis for Survival (Kaplan-Meier Method and Log-Rank Test)

Characteristics	Median Survival (months)			
	Progression-Free Survival (95% Confidence Interval)	*P* Value	OS (95% Confidence Interval)	*P* Value
Age (years)		0.84		0.66
≤60	39.9 (15.2—64.5)		54.5 (25.6—83.4)	
>60	35.7		35.7	
Sex		0.20		0.13
Male	17.8 (0.0—49.5)		NA	
Female	56.8		34.6 (0.0—72.0)	
Performance status		0.39		0.57
≤2	56.8 (37.0—76.6)		64.5 (26.6—102.4)	
>2	20.2 (0.0—44.8)		43.9 (11.6—76.2)	
Histology		0.48		0.97
DLBCL-non-GCB	42.5 (16.4—68.6)		64.5 (35.9—93.2)	
DLBCL-GCB	17.8 (4.3—31.2)		43.9 (20.0—65.8)	
DLBCL-NOS	15.6		30.6	
Natural killer/ T-cell lymphoma	NA		NA	
Deep brain lesions		0.50		0.48
Present	56.8 (24.5—89.5)		89.2 (27.9—150.6)	
Absent	35.7 (1.0—70.4)		38.5 (14.4—62.6)	
Number of lesions		0.41		0.07
1	42.5 (15.1—69.8)		80.7 (43.4—117.9)	
≥2	20.2 (0.0—41.6)		35.7 (21.4—50.1)	
Cerebrospinal fluid protein		0.15		0.58
Normal	3.7 (0.0—15.7)		NA	
Increased	58.4		80.7 (50.3—111.1)	
NA	35.7 (0.0—73.4)		43.9 (13.9—73.9)	
Lactate dehydrogenase		0.60		0.21
Normal	39.19 (21.2—58.5)		54.5 (22.6—86.4)	
Increased	20.2 (7.1—33.3)		34.7 (4.8—64.6)	
NA	86.1 (0.0—195.1)		89.2	
Rituximab		0.01*		0.02*
Yes	NA		NA	
No	16.3 (3.3—29.3)		35.7 (27.9—43.5)	
High-dose methotrexate				
>4 cycles	58.4 (29.3—87.5)	0.00*	80.7 (50.5—111.3)	0.00*
≤4 cycles	3.1 (2.4—3.7)		7.0 (3.8—10.2)	
Radiotherapy		0.48		0.37
Yes	42.5		80.7 (16.2—145.1)	
No	39.1 (13.5—64.8)		43.9 (18.1—69.8)	

NA, not applicable; DLBCL, diffuse large B cell lymphoma; GCB, germinal central B-cell like; NOS, non-special type.
*$P < 0.05$.

surgeons treated patients with PCNSL in the same way as other brain tumors. In our center, craniotomy is occasionally performed for symptomatic relief of severe mass effect or if the lesion has a similar imaging manifestation to other disease. Because neurosurgery techniques have developed during recent years, the value of craniotomy should be re-evaluated with new technological advancements such as fluorescent tumor visualization.[16,17] An exploratory analysis of the German PCNSL Study Group 1 (G-PCNSL-SG1) randomized trial has shown significantly better survival in patients with subtotal or gross total resections compared with biopsied patients.[18] Recently, Rae et al.[19] also reported a favorable association between craniotomy and survival, most pronounced in subgroups with favorable prognoses after a retrospective analysis of >9000 patients. However, it is not surprising that more resectable lesions may confer better prognosis irrespective of surgery type. Subsequent

Table 3. Multivariate Analysis for Survival

Covariates	Progression-Free Survival		Overall Survival	
	Hazard Ratio (95% Confidence Interval)	*P* Value	Hazard Ratio (95% Confidence Interval)	*P* Value
Age >60 years	0.79 (0.34—1.82)	0.58	1.29 (0.53—3.13)	0.58
Male vs. female	0.89 (0.44—1.76)	0.73	0.63 (0.30—1.33)	0.22
Performance status >2	1.1 (0.50—2.26)	0.87	0.79 (0.35—1.78)	0.57
Deep brain lesions	0.72 (0.34—1.49)	0.37	0.61 (0.25—1.48)	0.27
Multiple lesions	1.45 (0.69—3.1)	0.41	2.79 (1.08—7.2)	0.05
Rituximab	0.98 (0.43—2.24)	0.96	0.92 (0.39—2.19)	0.85
High-dose methotrexate >4 cycles	0.06 (0.02—1.15)	0.00	0.08 (0.03—0.21)	0.00
Radiotherapy	0.64 (0.31—1.30)	0.22	0.61 (0.27—1.37)	0.23

Table 4. Median Survival of Patients with Craniotomy or Stereotactic Biopsy

Methods	Single Lesion		Multiple Lesions	
	Progression-Free Survival (95% Confidence Interval)	Overall Survival (95% Confidence Interval)	Progression-Free Survival (95% Confidence Interval)	Overall Survival (95% Confidence Interval)
Total resection*	NA	NA	—	—
Partial resection	4.3 (0.0—9.1)	38.5 (0.0—91.6)	13.3 (0.0—37.4)	43.9 (0.0—89.1)
Stereotactic biopsy	NA	NA	35.7 (6.7—64.7)	35.7 (27.6—43.8)
P value	0.03	0.23	0.63	0.65

NA, not applicable.
*Total resection vs stereotactic biopsy $P = 0.65$.

treatment might also influence survival. Thus, future studies should focus on stratifying patients based on prognostic factors that likely influence survival after craniotomy.

Induction and Consolidation Therapy

The second controversial issue is the treatment strategy. Most treatments for PCNSL consist of induction and consolidation phases.[12] Polychemotherapy with HD-MTX $\geq$3 g/m^2 via a 3-hour infusion has become the backbone of the induction phase and the prognosis improves when HD-MTX is combined with other agents.[12] Numerous drugs such as procarbazine,[20,21] temozolomide,[5,22] and cytarabine[22,23] have been combined with HD-MTX to treat PCNSL as first-line chemotherapy in clinical trials. However, only temozolomide, cytarabine, and rituximab could be applied and covered by medical insurance in our hospital. Thus, these 3 drugs were combined with HD-MTX as first-line treatment in our cohort. Adding high-dose cytarabine either concurrently or sequentially to HD-MTX and administering marrow-ablative chemotherapy with hematopoietic salvage have been tried to improve the outcome of PCNSL.[12] Before January 2013, we tried to add high-dose cytarabine with or without rituximab to those fit patients, resulting in an overall response rate of 70.00% (with rituximab) and 83.3% (without rituximab) and satisfactory median PFS and OS (with rituximab, not applicable; without rituximab, 86.1 and 89.2 months, respectively). However, all patients had grade 3—4 toxicity. Temozolomide is an alkylating agent with good BBB penetration and low toxicity and has been reported to be active in relapsing and newly diagnosed PCNSL.[5,22,24-31] We have used temozolomide in our frontline setting since January 2013, resulting in an overall response rate of 88.00% (with rituximab) and 52.94% (without rituximab) and shorter median PFS and OS (with rituximab, 56.8 months and not applicable; without rituximab, 7.3 and 34.7 months, respectively).

The use of rituximab to treat PCNSL is another controversial issue because of its poor ability to penetrate the BBB.[32] The recent randomized phase 2 trial IELSG32[33] (International Extranodal Lymphoma Study Group-32) showed that the addition of rituximab to the combination of HD-MTX plus cytarabine was associated with an improvement in the overall response rate only. Houillier et al.[20] also reported that the addition of rituximab to a combination of MTX, procarbazine, vincristine, and intensified cytarabine consolidation was associated with improvement only in the overall response rate. Use of rituximab was optional in our cohort because of economic issues. Addition of rituximab was associated with an improvement of survival only in patients treated with HD-MTX and temozolomide. The synergistic effect of rituximab and temozolomide needs further exploration.

Consolidation therapy is also important for the treatment strategy. WBRT,[34] nonmyeloablative chemotherapy,[20] and high-dose chemotherapy with autologous stem cell support[8-10] are the most common options. WBRT is applied with caution regarding the high risk of delayed neurotoxicity because of the greater age of patients with PCNSL.[35] A randomized trial, named G-PCNSL-SG1,[36]

Table 5. Median Survival of Patients with Different Chemotherapy Regimens

Drugs	Progression-Free Survival (95% Confidence Interval, Months)			Overall Survival (95% Confidence Interval, Months)		
	+ Rituximab	− Rituximab	*P*	+ Rituximab	− Rituximab	*P*
HD-MTX	20.2 (13.4—27.0)	16.3 (9.8—22.8)	0.61	36.3 (23.8—48.7)	38.5 (9.1—68.0)	0.31
HD-MTX with cytarabine	NA	86.1 (31.8—140.5)	0.62	NA	89.2 (40.8—137.7)	0.63
HD-MTX with temozolomide	56.8	7.3 (0.0—15.7)	0.00	NA	34.7 (5.5—63.9)	0.00

HD-MTX, High-dose methotrexate; NA, not applicable.

Table 6. Survival of Patients with Different Maintenance or Consolidation Methods

Treatment	N	Median Survival (Months)	
		Progression-Free Survival (95% Confidence Interval)	Overall Survival (95% Confidence Interval)
Radiotherapy	15	86.1	89.2 (71.9—106.6)
Temozolomide	21	NA	NA
Monitoring	18	56.8 (19.8—93.7)	64.5
P value (log-rank test)		0.64	0.32

NA, not applicable.

compared WBRT with observation after chemotherapy. In this study, patients who achieved complete remission after HD-MTX, with or without ifosfamide, were randomly allocated between consolidating WBRT (45 Gy in 30 fractions) and observation. The use of WBRT was associated with a significantly better PFS, whereas there were no differences in OS. A recent prospective randomized trial, IELSG32, compared WBRT and autologous stem cell transplantation as consolidation options in patients with PCNSL responsive to HD-MTX—containing induction and showed no significant differences in 2-year PFS.[37] However, in our hospital, drugs for conditioning treatment before autologous stem cell transplantation such as carmustine, thiotepa, and melphalan are not available. Thus, autologous stem cell transplantation was not chosen as consolidation therapy in our cohort. WBRT (before January 2013) or temozolomide were used in those who had a response to HD-MTX treatment. Active monitoring was used in those who could not afford the cost of WBRT or temozolomide. In our cohort, no significant difference considering PFS and OS was seen among these 3 groups. However, 28.57% of patients with temozolomide maintenance and 40.0% of patients with radiotherapy relapsed in our cohort, suggesting that patients, especially those fit for autologous stem transplantation, might be undertreated in our cohort.

Patients with Refractory/Relapse PCNSL

Thirty-nine patients showed disease progression after or during first-line chemotherapy. These patients had a poor prognosis, with median second OS (calculated from the date of first disease progression to the time of death from any cause) of 7.2 months (95% CI, 2.5—12.00 months) (**Figure 2**). Novel agents are used in patients with relapse/refractory disease. MYD88 and CD79B are the most frequent mutations observed in PCNSL,[38] and thus, Bruton tyrosine kinase inhibition is an attractive treatment concept in PCNSL. Ibrutinib has induced meaningful chances for lymphoma regression in at least 50% of patients in relapse/refractory PCNSL.[39-41] However, remissions do not seem durable, with a median PFS of around 5 months and infection with *Aspergillus* is an important safety signal of ibrutinib in PCNSL.[39-41] The DA-TEDDI-R protocol (a dose-adjusted immune polychemotherapy protocol with

Table 7. Characteristics of Patients at First Relapse/Progression After First-Line Chemotherapy

Characteristics	N (%)
Age (years)	
≤60	30/39 (76.93)
>60	9/39 (23.07)
Sex	
Male	17/39 (43.59)
Female	22/39 (56.41)
Relapse site	
Central nervous system	37/39 (94.88)
Testicle	1/39 (2.56)
Systemic + central nervous system	1/39 (2.56)
Relapse time (years)	
≤1	27/39 (69.23)
>1	12/39 (30.77)
First-line treatment	
M	9/11 (81.82)
R-M	4/5 (80.00)
MA	3/6 (50.00)
R-MA	4/10 (25.00)
MT	12/17 (70.56)
R-MT	7/25 (28.00)
Consolidation/maintenance treatment	
Temozolomide	6/21 (28.57)
Radiotherapy	6/15 (40.00)
Active monitoring	8/18 (44.45)
Further treatment	
Lenalidomide	8/39 (20.51)
Ibrutinib	3/39 (7.69)
IE	7/39 (17.94)
MVP	4/39 (10.25)
Radiotherapy	17/39 (43.58)
High-dose methotrexate	6/39 (15.38)
Palliative care	3/39 (7.69)
CHOP	2/39 (5.13)

M, high-dose methotrexate; R, rituximab; MA, high-dose methotrexate with cytarabine; MT, high-dose methotrexate with temozolomide; IE, isophophamide with etopside; MVP, methotrexate, vincristine and procarbazine; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone.

temozolomide, etoposide, liposomal doxorubicin, dexamethasone, rituximab, and intrathecal cytarabine) was associated with a relatively high treatment-associated mortality of 17% with most patients

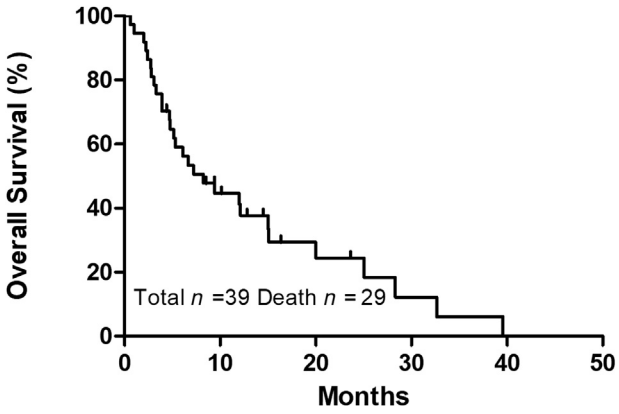


Figure 2. Survival of patients after first relapse/progression.

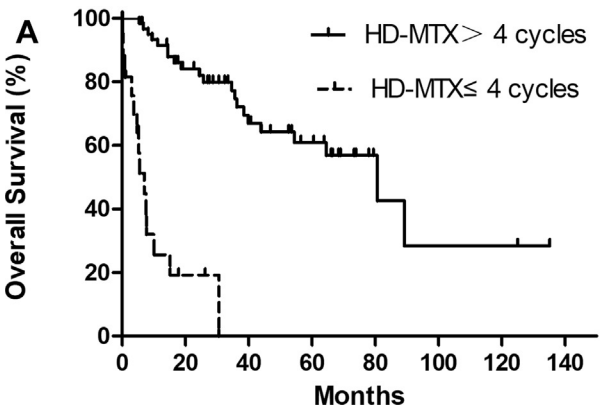
in good PS (72% with PS of 1).[40] It is unclear which component of DA-TEDDI-R has driven this high mortality. Thus, studies of combination protocols with ibrutinib must be cautious. Grommes et al. are undertaking a study investigating the combination of ibrutinib and HD-MTX (NCT02315326). Moreover, there is another ongoing study investigating ibrutinib maintenance treatment in the elderly with de novo PCNSL after achieving first remission (NCT02623010). In our cohort, 3 patients received ibrutinib and all showed a response to ibrutinib treatment without *Aspergillus* infection. We are trying to combine HD-MTX with ibrutinib as first-line therapy to treat those who are not fit for extensive chemotherapy and autologous stem cell transplantation, because ibrutinib is available in China. Other drugs such as lenalidomide and immune checkpoint inhibitor have also shown meaningful clinical activity in PCNSL.[42-44] Moreover, chimeric antigen receptor T cells have been shown to induce remission in a patient with lymphoma with central nervous system infiltration.[45] We still have no idea which patients can benefit from these drugs and thus validation of robust predictive biomarkers is important in PCNSL.

Prognostic Factors of PCNSL

The last controversial issue is the prognostic factor. The International Extra-Nodal Lymphoma Study Group reported a score system predicting the outcome for patients with PCNSL using age, PS, LDH serum level, cerebrospinal protein concentration, and involvement of deep structures of the brain.[46] However, this prognostic system has a limitation in that it was issued >10 years ago, and the treatment strategy has changed rapidly during recent years. In our cohort, survival was associated with none of these factors. The only factor affecting survival in multivariate analysis is the cycles of HD-MTX. As shown in **Figure 3**, those who received <5 cycles of HD-MTX had a poor prognosis. This group of patients might respond poorly to HD-MTX. Recent insights into PCNSL biology and its mutational landscape provide new hypotheses for potential predictive markers. In the future, there might be a prognostic factor system for PCNSL combining clinical parameters and biomarkers.

CONCLUSIONS

The outcomes of patients with PCNSL treated in our cohort are still poor. China is still a developing country. About 10% of patients in our cohort gave up treatment after diagnosis for economic reasons. Some patients could not afford the costs for intensive treatment and severe side effects. Moreover, many effective drugs are not accessible in China. Thus, it is difficult for physicians to work out a treatment strategy, resulting in the undertreatment of patients with PCNSL, especially young patients fit for autologous stem transplantation. Moreover, relapse or refractory PCNSL and those not tolerating aggressive chemotherapy urgently require new approaches to improve their still dismal prognosis. Novel agents such as ibrutinib have shown promising clinical activity. Future studies should focus on the predictive biomarkers for the treatment of PCNSL with novel agents to provide precision medicine for PCNSL.



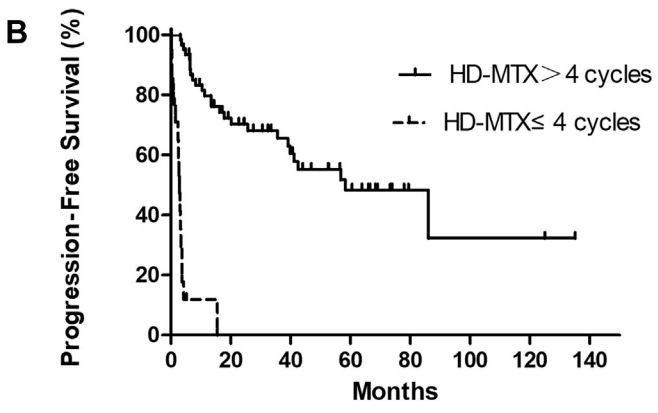


Figure 3. Comparison of patients treated with >4 cycles of high-dose methotrexate (HD-MTX) and ≤4 cycles of high-dose methotrexate. (**A**) Overall survival. (**B**) Progression-free survival.

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Conflict of interest statement: This article was supported by Guangdong Provincial Department of Science and Technology Fund Project (to W.L., grant number 2016A050502028).

Received 3 August 2018; accepted 4 October 2018

Citation: World Neurosurg. (2019) 123:e15-e24.
https://doi.org/10.1016/j.wneu.2018.10.034

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