Research Square

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Multicenter retrospective analysis of 118 cases of Primary Central Nervous System Diffuse Large B-Cell Lymphoma

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Abstract

Purpose

To retrospectively evaluate the efficacy of high-dose methotrexate (HD-MTX)-based regimens in patients with primary central nervous system diffuse large B-cell lymphoma (PCNS-DLBCL) and to assess the impact of consolidation with hematopoietic stem cell transplantation (HSCT) or maintenance therapy on long-term survival.

Methods

A total of 118 patients with PCNS-DLBCL treated between January 2016 and December 2023 were enrolled and assigned to five groups based on treatments: radiotherapy alone (n = 24), HD-MTX monotherapy (n = 17), HD-MTX plus temozolomide (n = 18), rituximab combined with HD-MTX and temozolomide or radiotherapy (n = 39), and rituximab–HD-MTX–temozolomide plus a Bruton's tyrosine kinase(BTK) inhibitor (n = 20).

Results

The median follow-up was 57 months. The four-drug group showed significantly longer overall survival (OS) and progression-free survival (PFS) than the other four groups (P = 0.0003 and P = 0.013, respectively). The objective response rate (ORR) after two cycles was also highest in the four-drug group (P = 0.016). Patients receiving BTK inhibitor-containing regimens had a better OS benefit (P = 0.008) and a trend toward improved PFS (P = 0.08). Post-induction strategies included HSCT consolidation (n = 16), maintenance therapy (n = 32), and observation (n = 70). Both HSCT and maintenance therapy were associated with prolonged OS compared with observation (P = 0.013 and P = 0.016, respectively); maintenance therapy also improved PFS (P = 0.033).

Conclusion

The four-drug regimen containing a BTK inhibitor demonstrated favorable efficacy and a high ORR after two cycles in PCNS-DLBCL. Post-induction HSCT or maintenance therapy may further improve survival outcomes. BTK inhibitor-containing regimens showed a promising trend toward long-term survival benefit, warranting further investigation.

1. Introduction

Primary central nervous system lymphoma (PCNSL) is a rare extranodal non-Hodgkin lymphoma (NHL), accounting for 2%–4% of all primary intracranial malignancies and 4%–6% of all NHL cases [1]. Pathologically, > 95% of PCNSLs are diffuse large B-cell lymphoma (DLBCL), predominantly of the non-germinal center B-cell (non-GCB) phenotype [2–4]. The disease is characterized by rapid progression, high mortality, and poor prognosis, with a long-term survival rate of only approximately 30% [2–4]. Although its precise pathogenesis remains incompletely understood, acquired immunodeficiency—particularly Epstein–Barr virus (EBV) and HIV infection—is a well-established risk factor [3].

Currently, no globally standardized first-line regimen exists for PCNSL, although most consensus guidelines recommend a sequence of induction, consolidation, and maintenance therapy [5]. Due to the chemosensitivity and radiosensitivity of PCNSL, and the ability of certain agents to cross the blood–brain barrier, high-dose methotrexate (HD-MTX)-based polychemotherapy remains the most widely used induction strategy [6, 7]. HD-MTX is the cornerstone of current therapy, improving response rates and prolonging survival; however, outcomes with HD-MTX alone remain suboptimal [8].

High-risk patients—particularly those with deep parenchymal lesions, elevated cerebrospinal fluid (CSF) protein, or high lactate dehydrogenase (LDH) levels—often respond poorly to conventional chemotherapy and experience early disease progression or relapse [8, 9]. These patients frequently present with complications such as hemiplegia or infection, which further compromise

their performance status and tolerance to treatment [8, 9]. The optimal combination partners for HD-MTX remain a matter of debate. Various agents have been investigated in combination, including rituximab, cytarabine, temozolomide, procarbazine, and vincristine [10]. Rituximab added to HD-MTX has been shown to improve ORR and prolong PFS and OS [8].

For younger patients, autologous stem cell transplantation (ASCT) following high-dose cytarabine-containing consolidation is a preferred strategy that may further extend survival [7]. More recently, agents targeting PCNSL-specific molecular pathways—such as BTK inhibitors, immunomodulatory drugs, and PI3K/mTOR pathway inhibitors—have shown promise in improving outcomes [11].

Given these challenges, more effective and tolerable regimens are urgently needed. In this multicenter retrospective study, we analyzed 118 patients with PCNS-DLBCL to evaluate the clinical outcomes of various HD-MTX-based regimens and to assess the survival impact of post-induction consolidation or maintenance strategies. Our findings may inform the selection of optimal first-line and post-induction therapies in this difficult-to-treat population.

2. Methods

2.1 Study Design and Participants

This multicenter retrospective study included patients with pathologically confirmed PCNS-DLBCL who were treated at the Department of Hematology, Zhujiang Hospital, Southern Medical University, and Guangdong Sanjiu Brain Hospital between April 2016 and December 2023. A total of 118 patients were enrolled.

Patients were categorized into five groups according to their induction regimen: (1) HD-MTX monotherapy; (2) HD-MTX plus temozolomide; (3) HD-MTX, temozolomide, with either rituximab or radiotherapy; (4) HD-MTX, temozolomide, rituximab, and a BTK inhibitor; and (5) radiotherapy alone. The group of HD-MTX, temozolomide, with either rituximab or radiotherapy combined two variant regimens (with rituximab or radiotherapy) for analysis, as both were used as intensification strategies during the study period.

2.2 Data Collection

The following clinical data were collected from medical records: (1) demographic information (sex, age, time of onset and diagnosis, ECOG performance status, and KPS score); (2) clinical manifestations; (3) pathological findings, including immunohistochemical markers (Ki-67, BCL-2, CD10, BCL-6, MUM-1, and c-myc) and pathological classification (germinal center B-cell [GCB] vs non-GCB); (4) laboratory parameters (complete blood count, LDH, CSF protein, liver and renal function tests); (5) imaging characteristics (number and distribution of lesions on CT/MRI/PET-CT); and (6) treatment details (radiotherapy, surgery, chemotherapy, targeted agents, and number of cycles).

2.3 Treatment Regimens

Among the 118 patients, 94 received HD-MTX-based induction chemotherapy, while 24 received radiotherapy alone. For patients receiving chemotherapy, HD-MTX was administered intravenously at 3.0–3.5 g/m² per cycle, repeated every 21 days for 4–6 cycles, with standard leucovorin rescue, urine alkalization, and adequate hydration. Temozolomide was given orally at 150 mg/m² daily on days 1–5 of each 21-day cycle. Rituximab was administered at 375 mg/m² intravenously on day 1 of each cycle. BTK inhibitors (including orelabrutinib or zanubrutinib) were given continuously at standard doses during induction. For patients in the radiotherapy-alone group, involved-field or whole-brain radiotherapy was delivered according to institutional protocols.

2.4 Efficacy Assessments

Tumor response was assessed by contrast-enhanced brain magnetic resonance imaging (MRI) after the second and fourth cycles of induction therapy. Responses were defined according to the International Primary CNS Lymphoma Collaborative Group (IPCG) criteria [12]. Complete response (CR) was defined as complete disappearance of all enhancing lesions, with no new lesions and no corticosteroid use. Partial response (PR) was defined as a ≥ 50% decrease in the sum of the perpendicular diameters of the largest enhancing lesion, without new lesions. Progressive disease (PD) was defined as a ≥ 25% increase in

lesion size or the appearance of new lesions. Stable disease (SD) was defined as a response that met neither PR nor PD criteria. The objective response rate (ORR) was calculated as (CR + PR) / total evaluable patients × 100%.

2.5 Safety Assessment

Adverse events (AEs) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. AEs included hematological toxicities (anemia, leukopenia, and thrombocytopenia) and non-hematological toxicities (hepatic and renal impairment, infection, and gastrointestinal reactions).

2.6 Follow-up and Endpoints

Follow-up data were collected through electronic medical records and telephone interviews. The cutoff date for follow-up was December 31, 2024. Overall survival (OS) was defined as the time from treatment initiation to death from any cause or last follow-up. Progression-free survival (PFS) was defined as the time from treatment initiation to disease progression, relapse, or death from any cause, whichever occurred first. Patients were censored at the time of last follow-up if no endpoint event had occurred.

2.7 Statistical Analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA). Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Univariable and multivariable Cox proportional hazards regression models were used to identify independent prognostic factors. Variables with $P < 0.10$ in univariable analysis were entered into the multivariable model. For multiple pairwise comparisons, P-values were adjusted using the Bonferroni correction where applicable. All tests were two-sided, and a P-value < 0.05 was considered statistically significant. Missing data were excluded from the denominator for percentage calculations and handled by pairwise deletion in regression analyses.

3. Result

3.1 Baseline Characteristics

The baseline demographic, clinical, and pathological characteristics of the 118 patients are summarized in Table 1. Briefly, the cohort comprised 67 male (56.8%) and 51 female (43.2%) patients, with a median age of 60 years (range, 21–79 years). The majority of patients (62.7%) had the non-GCB subtype. Deep intracranial structures—including the basal ganglia, corpus callosum, cerebellum, and periventricular white matter—were involved in 70.3% of patients. According to the International Extranodal Lymphoma Study Group (IELSG) prognostic score, 22.0% of patients were classified as low-risk, 64.4% as intermediate-risk, and 13.6% as high-risk. Between-group differences were observed in MSKCC risk stratification ($P = 0.029$) and the proportions of patients receiving maintenance therapy or HSCT ($P = 0.015$ and $P < 0.001$, respectively); other baseline characteristics were generally balanced across the five groups.

Table 1
Baseline demographic, clinical, and pathological characteristics of the five treatment groups.

	HD-MTX monotherapy group	HD-MTX combined with Temozolomide group	Rituximab combined with HD-MTX and temozolomide or radiotherapy	Four-drug group of rituximab, HD-MTX, temozolomide combined with BTK inhibitor	Radiotherapy alone group	Statistic	*P* value
	N = 17	N = 18	N = 39	N = 20	N = 24		
Sex						χ^2 = 1.686	0.793
Male	9 (52.94%)	8 (44.44%)	24 (61.54%)	12 (60.00%)	14 (58.33%)		
Female	8 (47.06%)	10 (55.56%)	15 (38.46%)	8 (40.00%)	10 (41.67%)		
Age						χ^2 = 5.134	0.274
≤ 60	9 (52.94%)	12 (66.67%)	22 (56.41%)	7 (35.00%)	10 (41.67%)		
> 60	8 (47.06%)	6 (33.33%)	17 (43.59%)	13 (65.00%)	14 (58.33%)		
KPS							0.129
< 70	2 (11.76%)	3 (16.67%)	13 (33.33%)	9 (45.00%)	5 (20.83%)		
≥ 70	15 (88.24%)	15 (83.33%)	26 (66.67%)	11 (55.00%)	19 (79.17%)		
MSKCC							0.029
Low risk	2 (11.76%)	9 (50.00%)	10 (25.64%)	2 (10.00%)	3 (12.50%)		
Intermediate-risk	13 (76.47%)	7 (38.89%)	19 (48.72%)	9 (45.00%)	16 (66.67%)		
High risk	2 (11.76%)	2 (11.11%)	10 (25.64%)	9 (45.00%)	5 (20.83%)		
Ki-67						χ^2 = 7.337	0.119
< 90	8 (47.06%)	8 (47.06%)	26 (68.42%)	15 (78.95%)	12 (50.00%)		
≥ 90	9 (52.94%)	9 (52.94%)	12 (31.58%)	4 (21.05%)	12 (50.00%)		
NA	0	1	1	1	0		
BCL-2							0.774
≤ 50	5 (29.41%)	4 (25.00%)	6 (16.22%)	3 (15.79%)	5 (20.83%)		
> 50	12 (70.59%)	12 (75.00%)	31 (83.78%)	16 (84.21%)	19 (79.17%)		
NA	0	2	2	1	0		
CD10						χ^2 = 6.797	0.147
≤ 30	14 (82.35%)	9 (52.94%)	23 (62.16%)	12 (63.16%)	20 (83.33%)		
> 30	3 (17.65%)	8 (47.06%)	14 (37.84%)	7 (36.84%)	4 (16.67%)		
NA	0	1	2	1	0		
BCL-6							0.533

	HD-MTX monotherapy group	HD-MTX combined with Temozolomide group	Rituximab combined with HD-MTX and temozolomide or radiotherapy	Four-drug group of rituximab, HD-MTX, temozolomide combined with BTK inhibitor	Radiotherapy alone group	Statistic	*P* value
	N = 17	N = 18	N = 39	N = 20	N = 24		
≤ 30	2 (11.76%)	3 (17.65%)	5 (13.51%)	6 (31.58%)	5 (20.83%)		
> 30	15 (88.24%)	14 (82.35%)	32 (86.49%)	13 (68.42%)	19 (79.17%)		
NA	0	1	2	1	0		
MUM-1							0.004
≤ 30	1 (5.88%)	9 (52.94%)	9 (24.32%)	1 (5.88%)	9 (37.50%)		
> 30	16 (94.12%)	8 (47.06%)	28 (75.68%)	16 (94.12%)	15 (62.50%)		
NA	0	1	2	3	0		
C-myc						χ^2 = 5.819	0.213
< 40	3 (17.65%)	6 (33.33%)	8 (20.51%)	9 (45.00%)	9 (37.50%)		
≥ 40	14 (82.35%)	12 (66.67%)	31 (79.49%)	11 (55.00%)	15 (62.50%)		
Tumor classification						χ^2 = 2.072	0.723
Non-GCB	12 (70.59%)	9 (52.94%)	23 (60.53%)	13 (68.42%)	17 (70.83%)		
GCB	5 (29.41%)	8 (47.06%)	15 (39.47%)	6 (31.58%)	7 (29.17%)		
NA	0	1	1	1	0		
Lactate dehydrogenase							0.839
Normal	11 (73.33%)	11 (68.75%)	29 (78.38%)	13 (68.42%)	16 (66.67%)		
Elevated	4 (26.67%)	5 (31.25%)	8 (21.62%)	6 (31.58%)	8 (33.33%)		
NA	2	2	2	1	0		
Cerebrospinal fluid protein levels							0.186
Normal	2 (50.00%)	5 (38.46%)	12 (42.86%)	4 (23.53%)	6 (75.00%)		
Elevated	2 (50.00%)	8 (61.54%)	16 (57.14%)	13 (76.47%)	2 (25.00%)		
NA	13	5	11	3	16		
Deep intracranial lesions						χ^2 = 2.751	0.600
Yes	10 (58.82%)	14 (77.78%)	27 (69.23%)	13 (65.00%)	19 (79.17%)		
No	7 (41.18%)	4 (22.22%)	12 (30.77%)	7 (35.00%)	5 (20.83%)		
ECOG score						χ^2 = 1.283	0.864

	HD-MTX monotherapy group	HD-MTX combined with Temozolomide group	Rituximab combined with HD-MTX and temozolomide or radiotherapy	Four-drug group of rituximab, HD-MTX, temozolomide combined with BTK inhibitor	Radiotherapy alone group	Statistic	*P* value
	N = 17	N = 18	N = 39	N = 20	N = 24		
< 2	9 (52.94%)	9 (50.00%)	19 (48.72%)	10 (50.00%)	9 (37.50%)		
≥ 2	8 (47.06%)	9 (50.00%)	20 (51.28%)	10 (50.00%)	15 (62.50%)		
IELSG score							0.149
Low risk	5 (29.41%)	3 (16.67%)	10 (25.64%)	4 (20.00%)	4 (16.67%)		
Intermediate-risk	12 (70.59%)	12 (66.67%)	26 (66.67%)	9 (45.00%)	17 (70.83%)		
High risk	0 (0.00%)	3 (16.67%)	3 (7.69%)	7 (35.00%)	3 (12.50%)		
Maintenance Therapy							0.015
No	16 (94.12%)	16 (88.89%)	29 (74.36%)	11 (55.00%)	14 (58.33%)		
Yes	1 (5.88%)	2 (11.11%)	10 (25.64%)	9 (45.00%)	10 (41.67%)		
Hematopoietic Stem Cell Transplantation							< 0.001
No	17 (100.00%)	18 (100.00%)	31 (79.49%)	12 (60.00%)	24 (100.00%)		
Yes	0 (0.00%)	0 (0.00%)	8 (20.51%)	8 (40.00%)	0 (0.00%)		

Data are presented as n (%). HD-MTX: high-dose methotrexate; BTK: Bruton's tyrosine kinase; KPS, Karnofsky Performance Status; MSKCC, Memorial Sloan Kettering Cancer Center; NA, not available; GCB, germinal center B-cell; ECOG, Eastern Cooperative Oncology Group; IELSG, International Extranodal Lymphoma Study Group; HSCT, hematopoietic stem cell transplantation. χ^2: Chi-square test, P values < 0.05 were considered statistically significant.

3.2 Short-term Efficacy

Efficacy was evaluated after the second and fourth induction cycles. The ORR and response distribution for each group are summarized below. At cycle 2, the ORR ranged from 56.3% in the monotherapy group to 100% in the quadruple group, with a statistically significant difference across the five groups (P = 0.016). At cycle 4, the ORR ranged from 80.0% to 100%, with no significant between-group difference (P = 0.183). The quadruple group consistently achieved the highest ORR at both time points (100% at cycle 2 and 94.4% at cycle 4).

3.3 Survival Outcomes

As of December 31, 2024, 84 patients had died, primarily due to disease progression or recurrence. The median follow-up duration was 57 months. Median OS and PFS for each group are summarized in Table 2. The quadruple group had the longest median OS (40 months) and PFS (40 months), while the doublet group had the shortest (17.5 and 9.5 months, respectively). Kaplan–Meier analysis revealed statistically significant differences among the five groups for both OS (P = 0.0003) and PFS (P = 0.013) (Fig. 1a,b).

Table 2
Overall survival and progression-free survival among the five treatment groups.

Treatment group	Number of patients	OS events, n	Median OS, months	PFS events, n	Median PFS, months
HD-MTX monotherapy	17	17	20	17	13
HD-MTX combined with temozolomide	18	18	17.5	16	9.5
Rituximab combined with HD-MTX and temozolomide or radiotherapy	39	25	31	27	20
Rituximab, HD-MTX, temozolomide combined with BTK inhibitor	20	4	40[a]	8	40[a]
Radiotherapy alone	24	20	18	20	18
Log-rank P value			0.0003		0.013

[a]The median OS and PFS of the quadruplet group were reached with only 4 OS and 8 PFS events among 20 patients and should be interpreted with caution.

The five groups correspond to the monotherapy, doublet therapy, triplet therapy, quadruplet therapy, and radiotherapy groups in Table 3. Abbreviations: *OS*, overall survival; *PFS*, progression-free survival; HD-MTX, high-dose methotrexate; BTK, Bruton tyrosine kinase.

3.4 Safety Profile

All AEs were grade 1–2 according to CTCAE version 4.0, and no treatment-related deaths occurred. The most common AE was hepatic impairment (63.6%, n = 75), followed by anemia (53.4%, n = 63), infection (41.5%, n = 49), renal impairment (32.2%, n = 38), leukopenia (18.6%, n = 22), thrombocytopenia (17.8%, n = 21), and gastrointestinal reactions (5.9%, n = 7). The incidence of AEs across the five groups is detailed in Table 3. Except for infection, which was significantly more frequent in the radiotherapy group (P = 0.006), the differences in other AEs between groups were not statistically significant (all P > 0.05).

Table 3
Comparison of treatment-related adverse events among the five treatment groups.

Variables	Total (n = 118)	Monotherapy (n = 17)	Doublet therapy (n = 18)	Triplet therapy (n = 39)	Quadruplet therapy (n = 20)	Radiotherapy (n = 24)	Statistic	*P* value
Leukopenia, n(%)							-	0.321
No	96 (81.36)	16 (94.12)	13 (72.22)	29 (74.36)	17 (85.00)	21 (87.50)		
Yes	22 (18.64)	1 (5.88)	5 (27.78)	10 (25.64)	3 (15.00)	3 (12.50)		
Anemia, n(%)							χ^2 = 2.56	0.634
No	55 (46.61)	10 (58.82)	8 (44.44)	17 (43.59)	11 (55.00)	9 (37.50)		
Yes	63 (53.39)	7 (41.18)	10 (55.56)	22 (56.41)	9 (45.00)	15 (62.50)		
Thrombocytopenia, n(%)							-	0.408
No	97 (82.20)	15 (88.24)	15 (83.33)	28 (71.79)	18 (90.00)	21 (87.50)		
Yes	21 (17.80)	2 (11.76)	3 (16.67)	11 (28.21)	2 (10.00)	3 (12.50)		
Liver impairment, n(%)							χ^2 = 1.24	0.872
No	43 (36.44)	5 (29.41)	6 (33.33)	15 (38.46)	9 (45.00)	8 (33.33)		
Yes	75 (63.56)	12 (70.59)	12 (66.67)	24 (61.54)	11 (55.00)	16 (66.67)		
Kidney damage, n(%)							χ^2 = 5.45	0.244
No	80 (67.80)	14 (82.35)	11 (61.11)	26 (66.67)	16 (80.00)	13 (54.17)		
Yes	38 (32.20)	3 (17.65)	7 (38.89)	13 (33.33)	4 (20.00)	11 (45.83)		
Infection, n(%)							χ^2 = 14.55	0.006
No	69 (58.47)	10 (58.82)	11 (61.11)	22 (56.41)	18 (90.00)	8 (33.33)		
Yes	49 (41.53)	7 (41.18)	7 (38.89)	17 (43.59)	2 (10.00)	16 (66.67)		

Variables	Total (n = 118)	Monotherapy (n = 17)	Doublet therapy (n = 18)	Triplet therapy (n = 39)	Quadruplet therapy (n = 20)	Radiotherapy (n = 24)	Statistic	*P* value
Gastrointestinal reactions, n(%)							-	0.323
No	111 (94.07)	17 (100.00)	18 (100.00)	36 (92.31)	17 (85.00)	23 (95.83)		
Yes	7 (5.93)	0 (0.00)	0 (0.00)	3 (7.69)	3 (15.00)	1 (4.17)		

Monotherapy: HD-MTX alone; Doublet therapy: HD-MTX combined with temozolomide; Triplet therapy: rituximab combined with HD-MTX and temozolomide or radiotherapy; Quadruplet therapy: rituximab, HD-MTX, and temozolomide combined with a Bruton tyrosine kinase inhibitor; Radiotherapy: radiotherapy alone. HD-MTX, high-dose methotrexate. χ^2: Chi-square test, -: Fisher exact; P values < 0.05 were considered statistically significant.

3.5 Maintenance Therapy

Among the 118 patients, 32 received maintenance therapy after induction (orelabrutinib in 17, temozolomide in 14, and lenalidomide in 1), while 86 did not. Patients receiving maintenance therapy had significantly longer OS (P = 0.016) and PFS (P = 0.033) than those who did not (Fig. 1c,d).

3.6 Hematopoietic Stem Cell Transplantation (HSCT)

Only 16 of the 118 patients underwent HSCT consolidation. Survival analysis showed a significant OS benefit for the transplant group compared with the non-transplant group (P = 0.013). Although PFS was longer in the transplant group, the difference did not reach statistical significance (P = 0.11; Fig. 1e,f).

3.7 Targeted Therapy

A total of 20 patients received BTK inhibitor-containing regimens (13 male, 7 female; age range, 40–77 years). In this group, the ORR was 100% (18/18) at cycle 2 and 94.4% (17/18) at cycle 4. By the cutoff date, 4 patients had died. Patients receiving BTK inhibitor-based therapy had significantly longer OS compared with those receiving conventional regimens (P = 0.008), with a trend toward PFS benefit that did not reach statistical significance (P = 0.08) (Supplementary Fig. 1).

4. Discussion

As a rare type of non-Hodgkin lymphoma (NHL), PCNSL accounts for 2% to 4% of all primary malignant tumors of the brain and central nervous system. It can occur in the brain, brainstem, meninges, cerebellum, spinal cord, and eyes [13]. As a rare extranodal NHL, PCNSL is characterized by rapid progression, a high risk of recurrence, a poor prognosis, and short survival. In recent years, its incidence has been increasing, particularly among the elderly [14]. More than 95% of PCNSL patients have DLBCL.

In this study, the median age at diagnosis was 60 years, and the proportion of male patients was slightly higher than that of female patients. Lesions primarily involved deep brain structures such as the basal ganglia, corpus callosum, cerebellum, and periventricular structures. All enrolled cases were pathologically classified as DLBCL, with the non-GCB subtype being the predominant type, accounting for 62.71%. The most common symptoms at disease onset were related to increased intracranial pressure and neurological dysfunction, primarily including headache, dizziness, nausea and vomiting, memory impairment, ataxia, sensory abnormalities, and cognitive impairment; a minority presented with blurred vision, altered consciousness, or seizures.

In summary, the clinical heterogeneity of PCNSL underscores the importance of early recognition. For patients presenting with unexplained focal neurological deficits, progressive cognitive impairment or visual disturbances, clinicians should be alert to the

possibility of PCNSL, promptly perform imaging studies such as cranial MRI for initial screening, and confirm the diagnosis through histopathological examination.

Although there is currently no standard first-line treatment regimen for PCNSL, various therapeutic approaches have been attempted, including surgery, chemotherapy, radiotherapy, immunotherapy, targeted therapy, and HSCT. However, the optimal treatment regimen still requires further exploration [15]. HD-MTX-based combination chemotherapy regimens are currently the most commonly used treatment options in clinical practice [16, 17], but their benefits for PCNSL remain limited; there is an urgent need for more effective combination treatment strategies to improve the prognosis of patients receiving first-line therapy.

With the continued advancement of precision medicine, targeted therapy strategies have brought new hope for improving the prognosis of patients with PCNSL. Rituximab is a human-mouse chimeric monoclonal antibody that targets the CD20 antigen and is currently a first-line drug in the standard treatment regimen for diffuse large B-cell lymphoma. Due to its large molecular weight, when the blood-brain barrier is intact, the concentration of rituximab in cerebrospinal fluid is only 0.1%–0.4% of its plasma concentration; however, in patients with PCNSL, tumor infiltration causes localized disruption of the blood-brain barrier, allowing small amounts of rituximab to enter the central nervous system and exert an antitumor effect [8]. Studies have shown that adding rituximab to HD-MTX significantly improves the ORR in patients with PCNSL and prolongs PFS and OS [8]. A retrospective study conducted by Holdhoff et al. enrolled 81 treatment-naive PCNSL patients, of whom 54 received HD-MTX monotherapy (control group) and 27 received HD-MTX combined with rituximab (experimental group); The combination group showed a significantly higher complete remission rate (73% vs. 36%) and significantly prolonged both median OS and median PFS [18].

Temozolomide, a novel alkylating antitumor agent, is converted into active metabolites via non-enzymatic pathways in the body, inducing DNA methylation in tumor cells and leading to mismatch repair failure, thereby exerting its cytotoxic effect. This agent readily crosses the blood-brain barrier and has been widely used in the clinical treatment of gliomas. In recent years, its value in the treatment of lymphoma—particularly PCNSL—has increasingly been recognized [19, 20]. Studies both domestically and internationally have begun to evaluate the efficacy of the HD-MTX combined with temozolomide regimen in PCNSL. In a Phase II multicenter clinical trial (CALGB 50202), a total of 44 PCNSL patients were enrolled; with a median follow-up of 4.9 years, 29 patients achieved complete remission (CR), and the progression-free survival (PFS) was 2.4 years [21]. Another Phase II clinical study explored the value of temozolomide during the maintenance phase in elderly PCNSL patients, providing new insights into treatment strategies for this population [22].

In recent years, given the unique molecular mechanisms of PCNSL, several novel targeted therapies have been introduced. Among these, BTK inhibitors, drugs targeting the PI3K/mTOR signaling pathway, and immunomodulators have attracted significant attention [11]. The development and application of these drugs signify that the treatment of PCNSL is gradually shifting from traditional chemotherapy toward precision therapy based on molecular subtyping.

In this study, 118 patients with PCNSL were stratified according to treatment strategy into the single-agent group (n = 17), the two-drug group (n = 18), the three-drug group (n = 39), the four-drug group (n = 20), and the radiotherapy-alone group (n = 24). Subgroup analysis revealed that the four-drug group had significantly better OS and PFS than the other four groups (P-values of 0.0003 and 0.013, respectively). In addition, the ORR after two treatment cycles in the four-drug group was significantly higher than in the other groups (P = 0.016), indicating that the four-drug combination therapy yields favorable short-term outcomes. However, the difference in ORR after four treatment cycles did not reach statistical significance (P = 0.183).

This study demonstrates that, in treatment-naive PCNSL patients, HD-MTX-based intensive combination regimens—particularly the four-drug RMTO regimen containing orelabrutinib—offer superior survival benefits and early efficacy compared to conventional regimens. The advantages of the RMTO group in terms of 1-year and 2-year OS, PFS, and early ORR provide preliminary support for the therapeutic rationale of multi-target synergy: rituximab mediates ADCC effects, HD-MTX and temozolomide exert cytotoxic effects, and orelabrutinib crosses the blood-brain barrier to sustain BCR pathway inhibition, acting synergistically on tumor cells and the immune microenvironment. This finding aligns with current research trends in combination therapy with BTK inhibitors and provides clinical evidence for optimizing first-line treatment strategies. Due to limitations of the retrospective design, sample size, and follow-up duration, the difference in ORR after four cycles did not reach

statistical significance, which may have been influenced by early discontinuation or assessment timepoints. Prospective, multicenter, randomized controlled trials are needed to further validate the long-term efficacy and safety of the RMTO regimen and to identify the appropriate patient population.

Molecular studies have confirmed that the abnormal activation of the B-cell receptor (BCR) and Toll-like receptor signaling pathways, as well as immune evasion mechanisms, are key factors in the pathogenesis of PCNSL [23]. Among these, high-frequency mutations in the CD79B and MYD88 genes are the primary drivers of the sustained activation of these pathways [23–25]. Bruton's tyrosine kinase (BTK), as a central signaling molecule in the BCR signaling pathway, is essential for B-cell development, survival, and functional maintenance [26]. Therefore, BTK inhibitors can effectively suppress lymphoma growth by blocking BCR signaling, inhibiting downstream inflammatory pathways, disrupting B-cell migration and adhesion, and ultimately inducing tumor cell apoptosis.

A retrospective study evaluated the efficacy of the BTK inhibitor orelabrutinib as monotherapy for PCNSL, with a six-month overall survival (OS) rate of 100% [27]. A retrospective study also found that treatment regimens containing BTK inhibitors demonstrated good efficacy in treatment-naive PCNSL patients; all patients achieved a best response of CR, with an ORR of 100% and a CR rate of 83.3% at the interim assessment [28]. Furthermore, multiple studies have confirmed that BTK inhibitors with higher CSF concentrations demonstrate superior efficacy in combination therapy for CNSL [27, 29]. Orelabrutinib, currently recognized as the BTK inhibitor with the highest kinase selectivity, not only has high bioavailability but also achieves higher CSF concentrations than ibrutinib, making it a promising superior option for treating CNSL.

Among the 118 patients in this study, 20 treatment-naive PCNSL patients received RMTO-based four-drug induction, with an ORR of 100% (18/18) after two cycles and 94.4% (17/18) after four cycles. Survival analysis showed a statistically significant difference in OS between patients treated with BTK inhibitors and those treated with conventional regimens (P = 0.008); PFS also demonstrated a trend toward benefit (P = 0.08). Survival curves showed a gradual divergence emerged between two groups, but no significant statistical difference was observed in PFS. This may be related to the low incidence of PCNSL, the small sample size, and insufficient follow-up duration, resulting in inadequate statistical power. Additionally, the occurrence of an endpoint event in the patient with the longest follow-up may also have influenced the tail of the survival curve and the statistical results. These findings require validation in larger studies with longer follow-up.

Furthermore, as PCNSL carries a high risk of recurrence, consolidation and maintenance therapy following induction chemotherapy are essential for long-term survival; therefore, the choice of regimen warrants careful consideration. Whole-brain radiotherapy and ASCT are commonly used as consolidation therapies for PCNSL [16, 30]. A retrospective study found that combination chemotherapy based on HD-MTX, followed by whole-brain radiotherapy, increases the risk of delayed neurotoxicity, leading to severe cognitive impairment and gait disturbances that impair quality of life; therefore, caution is warranted when using this approach in elderly patients [31]. Due to these adverse effects, many patients refuse to undergo whole-brain radiotherapy.

ASCT plays a crucial role in the consolidation treatment of PCNSL [29]; it can serve as first-line consolidation therapy for newly diagnosed patients achieving remission, as well as rescue therapy for patients with relapsed or refractory disease following remission after salvage chemotherapy [32]. The median age at diagnosis for PCNSL is 65 years; elderly patients frequently have comorbidities and poor prognosis. For younger patients (≤ 65–70 years) with newly diagnosed PCNSL, high-dose chemotherapy based on thiotepa followed by ASCT has become a standard first-line treatment, with 4-year OS rates up to 80% [33]. However, evidence of this regimen in elderly patients with good performance status remains limited. Recently, a Phase II single-arm study evaluated high-dose chemotherapy followed by HSCT in elderly PCNSL patients with good performance status, reporting a 12-month PFS rate of 58.8% [31, 33].

In this study, only 16 of the 118 patients underwent HSCT. The results showed OS significantly better between patients who underwent transplantation and those who did not (p = 0.013), while PFS also showed a trend toward benefit (p = 0.11). These results demonstrate the feasibility of HSCT in improving patients' quality of life and prolonging survival. However, the application of this regimen is limited by the high cost and the inability of patients with organ dysfunction to tolerate the pre-transplant

conditioning. Given that PCNSL predominantly affects elderly patients who may have organ impairment, HSCT has inherent limitations.

For patients ineligible for whole-brain radiotherapy or HSCT, maintenance therapy is particularly important. In this study, 32 patients who completed induction therapy and achieved CR received maintenance therapy with a BTK inhibitor, lenalidomide, and temozolomide. Significant differences were observed in PFS (P = 0.033) and OS (P = 0.016). These findings suggest that BTK inhibitors may be a viable option for maintenance therapy; however, the small sample size and short follow-up period limit the interpretation of these results.

When evaluating the clinical benefits of the aforementioned treatment regimens, it is essential to assess and manage treatment-related AEs and long-term toxicity. Effective management of adverse effects is critical to balancing the benefits and risks, ensuring treatment continuity, and preserving quality of life. High-dose methotrexate achieves therapeutic intracellular concentrations by increasing its plasma levels, effectively crossing the blood-brain barrier; however, this may also cause significant toxicity, such as myelosuppression, mucositis, acute hepatic and renal dysfunction, and gastrointestinal reactions. Toxicities associated with traditional HD-MTX regimens—particularly Grade 3–4 hematologic toxicities—require particular attention, as they increase the risk of infection, bleeding, and often necessitate treatment discontinuation [34]. Although non-hematologic toxicities with combination regimens are similar to those of monotherapy and generally manageable, common events such as hypokalemia, respiratory tract infections, and liver function abnormalities require close monitoring and management, along with timely intervention.

In this retrospective study, adverse events included both hematologic and non-hematologic categories; all were CTCAE Grade 1–2, and were well tolerated by most patients. Anemia was the most common hematologic toxicity (63 cases, 53.39%), followed by thrombocytopenia and leukopenia; these resolved with appropriate supportive care. Common non-hematologic events included liver function abnormalities, renal impairment, infections, and gastrointestinal reactions, which were generally manageable with symptomatic treatment; no treatment-related deaths occurred. Although the three-drug group had a higher incidence of AEs, the differences between the groups were not statistically significant (all P-values > 0.05), except for infection (P < 0.01).

Combining a BTK inhibitor, radiotherapy, or other chemotherapeutic agents with HD-MTX results in safety and tolerability comparable to HD-MTX monotherapy, without significantly increasing toxicity. These findings support the safety of this combination strategy and provide a promising new direction for the comprehensive treatment of PCNSL. However, long-term safety and applicability across different populations require validation in larger, multicenter, prospective studies. Future research should focus on tolerability management, resistance mechanisms, and the systematic assessment of long-term AEs, to support the safe and appropriate use of BTK inhibitors in PCNSL.

This multicenter retrospective study has several limitations, including selection bias, a non-randomized design, relatively short follow-up, and low rates of HSCT and maintenance therapy. These findings require validation in prospective studies with longer follow-up. Although HD-MTX-based combination chemotherapy has improved PCNSL prognosis, overall outcomes remain poor. Future strategies should focus on optimizing first-line treatment to reduce refractory disease. BTK inhibitor-containing four-drug regimens have shown advantages in short-term disease control and safety; however, given the critical location of PCNSL, timely and adequate treatment is essential, as delays or insufficient treatment may lead to rapid tumor spread or recurrence. Therefore, selecting an appropriate first-line regimen, initiating treatment early, and implementing consolidation and maintenance after induction are critical for prolonging survival and improving quality of life.

For relapsed/refractory PCNSL, chimeric antigen receptor T-cell (CAR-T) immunotherapy has shown potential curative value. Several small studies have reported on the efficacy and safety of CAR-T in PCNSL, suggesting that PCNSL is not a contraindication for CAR-T therapy. A recent French study analyzed anti-CD19 CAR-T therapy in relapsed/refractory PCNSL using the Eye-Brain Lymphoma Network (LOC) database [35]. Anti-CD19 CAR-T therapy is highly effective in heavily pretreated relapsed/refractory PCNSL, with CR rates as high as 86%. In third-line or later treatments, 46% of patients achieved long-term remission. Although these outcomes are encouraging, large-scale evaluation is still needed. Ongoing randomized trials evaluating rituximab, immunotherapy, targeted therapy, HSCT, radiotherapy, maintenance therapy, and CAR-T therapy are

expected to further improve PCNSL outcomes. Future research should focus on more precise, effective, and less toxic personalized regimens.

Declarations

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

Approved by the Ethics Committees of Zhujiang Hospital, Southern Medical University consistent with the precepts of the Helsinki Declaration and Institutional Review Boards of each participating center. Requirement for informed consent was waived and registered at ClinicalTrails.gov, MR-44-26-006809.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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Author Contribution

Conceptualization: all authors; Methodology: Minting Ye, Yanni Deng, Mingyao Lai, Haishan He, Linbo Cai, Yuhua Li, Shaojie Wu; Formal analysis and investigation: Minting Ye, Yanni Deng, Mingyao Lai, Haishan He, Jingwen Du, Lenghe Zhang, Rui Huang, Sanfang Tu, Sufen Jiang; Writing - original draft preparation: Minting Ye, Yanni Deng, Mingyao Lai, Haishan He, Linbo Cai, Yuhua Li, Shaojie Wu; Writing - review and editing: all authors; Supervision: Linbo Cai, Yuhua Li, Shaojie Wu. All authors read and approved the final manuscript.

Data Availability

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

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Figures

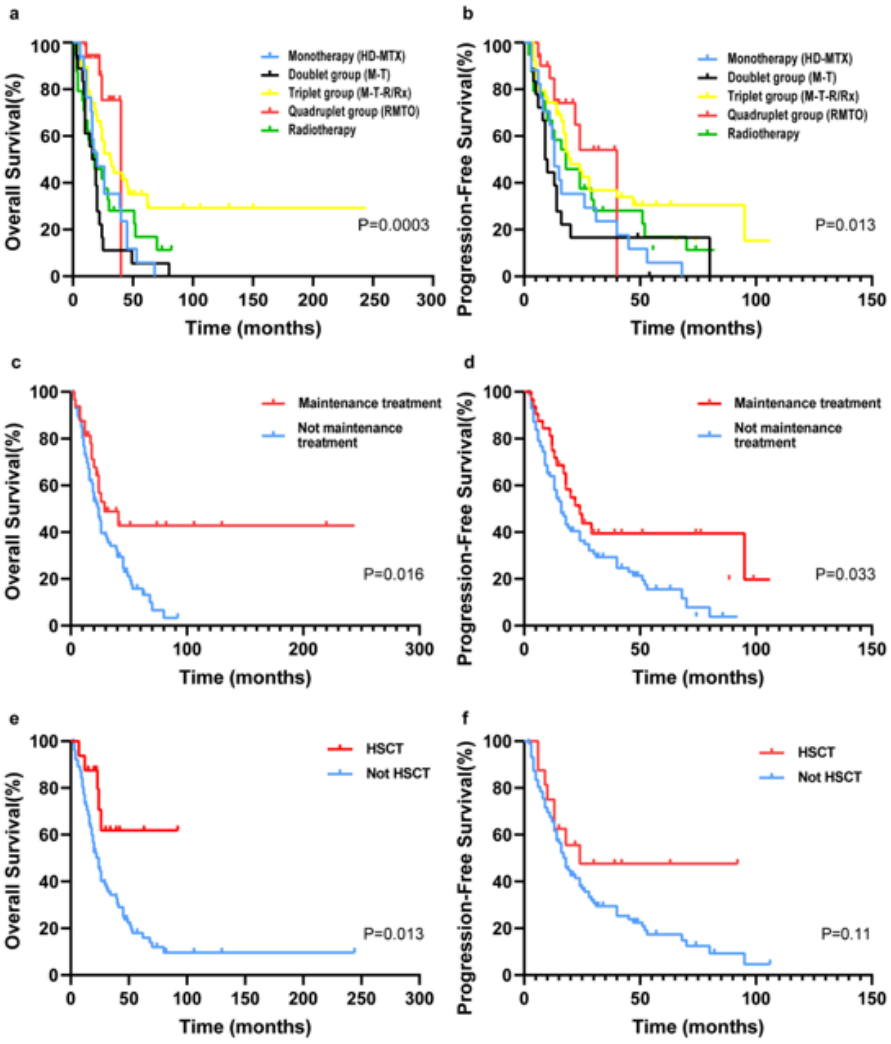


Figure 1

OS and PFS analysis across different treatment subgroups. Kaplan-Meier curves for (a, c, e) OS and (b, d, f) PFS. Comparisons include (a, b) different treatment regimens, (c, d) maintenance versus no maintenance treatment, and (e, f) HSCT versus no HSCT. The left column shows the total cohort, and the right column shows the corresponding subgroup analyses.

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