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ABOUT COVER

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Retrospective Study

Clinical outcomes of newly diagnosed primary central nervous system lymphoma treated with zanubrutinib-based combination therapy

Ning Wang, Fei-Li Chen, Lu Pan, Yan Teng, Xiao-Juan Wei, Han-Guo Guo, Xin-Miao Jiang, Ling Huang, Si-Chu Liu, Zhan-Li Liang, Wen-Yu Li

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Abstract

BACKGROUND

High-dose methotrexate (HD-MTX) combined with other chemotherapeutic agents is an effective treatment for patients with newly diagnosed primary central nervous system lymphoma (PCNSL); however, some patients have adverse reactions.

AIM

To retrospectively evaluate disease outcomes and mutational profiles in newly diagnosed PCNSL patients treated with a zanubrutinib/HD-MTX combination regimen.

METHODS

Nineteen newly diagnosed PCNSL patients were treated with zanubrutinib/HD-MTX until disease progression, intolerable toxicities, or physician/patient-directed withdrawal. Safety and efficacy were assessed per the CTCAE v5.0 and RECIST v1.1 criteria, respectively. The primary endpoint was the objective response rate (ORR), and the secondary endpoints were progression-free survival, overall survival (OS), and safety.

RESULTS

The median follow-up duration was 14.7 mo (range, 3.9–30 mo). The ORR for all patients was 84.2%, and 2-year progression-free- and OS rates were 75.6% and 94.1%, respectively. All patients completed the induction phase, and nine patients

underwent autologous stem cell transplantation as consolidation therapy, resulting in an ORR of 88.9%. Ten patients received zanubrutinib as maintenance therapy and achieved an ORR of 80%. All patients showed an acceptable safety profile. The sequencing results for cerebrospinal fluid (CSF) and tumor tissue showed that PIM1 mutations were the most frequent genetic alterations. Circulating tumor DNA was correlated with disease relapse and response.

CONCLUSION

Our empirical observations demonstrated that the combination of zanubrutinib with HD-MTX yielded a marked clinical response and tolerability among newly diagnosed PCNSL patients. Non-invasive CSF liquid biopsy profiling may be feasible for evaluating treatment response and tumor burden.

Key Words: Zanubrutinib; High-dose methotrexate; Primary central nervous system lymphoma; Liquid biopsy; Circulating tumor DNA

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Core Tip: Zanubrutinib combined with high-dose methotrexate provided a marked clinical response and tolerance in newly diagnosed primary central nervous system lymphoma patients. Additionally, the detection of circulating tumor DNA in cerebrospinal fluid played a significant part in disease surveillance and treatment response monitoring. However, given the small sample size and retrospective nature of this study, further research is required to validate our findings.

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INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an aggressive lymphoma that is confined to the brain, leptomeninges, eyes, cerebrospinal fluid (CSF), or spinal cord, without evidence of systemic disease[1,2]. Almost all PCNSLs constitute diffuse large B-cell lymphoma (DLBCL)[3]. However, the treatments for PCNSL and DLBCL differ. High-dose methotrexate (HD-MTX) is the primary treatment for PCNSL. HD-MTX (3.5 g/m²) combined with other chemotherapeutic agents is effective; however, some patients have adverse reactions[4,5]. Therefore, it is necessary to identify drugs that can be combined with HD-MTX to solve this issue.

Zanubrutinib, a novel oral inhibitor of Bruton's tyrosine kinase (BTK), is a promising therapeutic intervention in B-cell antigen receptor (BCR) and Toll-like receptor (TLR) signaling. This signaling network integrates signals from the BCR and TLR pathways. The key players, BCR-associated protein CD79B and myeloid differentiation primary response 88 (MYD88), act as bridges linking interleukin-1 and TLRs with the potent nuclear factor kappa B pathway[6-9]. Activating mutations were observed in MYD88 and CD79B across various studies of PCNSL[6,10-13]. Studies have shown that BTK inhibitors can cross the blood-brain barrier and effectively modulate signaling cascades downstream of MYD88 and CD79B[14-17], demonstrating their potential efficacy in PCNSL. Recent studies on zanubrutinib-containing therapeutic regimens have highlighted their effectiveness in cases of DLBCL with CNS involvement[18]. However, despite these advancements, a critical gap remains: the absence of concrete clinical evidence supporting the use of zanubrutinib in PCNSL with CNS involvement. The BTK inhibitor, ibrutinib, combined with HD-MTX has demonstrated an objective response rate (ORR) of 80% with an acceptable safety profile in a phase Ib study[19]. Therefore, we retrospectively analyzed the clinicopathological characteristics, treatment outcomes, and adverse events in newly diagnosed PCNSL patients treated with combined HD-MTX and zanubrutinib. We also explored the next-generation sequencing of circulating tumor DNA (ctDNA) in CSF, both before and during treatment, as well as the safety profile, treatment response, and genomic biomarkers.

MATERIALS AND METHODS

Patients

From May 2020 to April 2022, 19 eligible PCNSL patients from XX Hospital, China, were identified for inclusion in this study. The inclusion criteria were as follows: (1) Newly diagnosed pathologically confirmed PCNSL; (2) ≥ 18 years of age; (3) Treatment with HD-MTX and zanubrutinib combination therapy; and (4) Received at least two cycles of chemotherapy. The exclusion criteria were as follows: (1) Non-primary CNS lymphoma; (2) Previous treatment with other BTK

inhibitors; and (3) Patients with incomplete follow-up data, for whom we were unable to evaluate efficacy. The selection criteria are also shown in [Figure 1](#).

This study was approved by the Clinical and Research Ethics Committee of the Guangdong Provincial People's Hospital, Guangzhou, China. All procedures in the present study that involved human participants were performed in accordance with the Declaration of Helsinki. All patients provided written informed consent to participate in this study.

Treatment protocol

The treatment regimen was designed to achieve optimal outcomes through induction therapy with combined HD-MTX and zanubrutinib. HD-MTX was administered at a dose of 3.5 g/m², with a total of 4-8 doses planned. Zanubrutinib was prescribed at a dose of 160 mg orally (PO) twice daily (BID). Zanubrutinib administration was paused on the days of HD-MTX infusion to mitigate potential interactions and was resumed once HD-MTX clearance was achieved. Following induction therapy, zanubrutinib was administered as maintenance therapy until specific endpoints were reached, namely disease progression, intolerable toxicity, autologous stem cell transplantation (ASCT), or mortality.

Stem cell assessment and ASCT

Prior to ASCT, a comprehensive evaluation of each patient's stem cell composition was performed. The ASCT process comprised the use of peripheral blood autologous hematopoietic stem cells. To prepare patients for ASCT, a pre-conditioning regimen was administered that comprised either carmustine, etoposide, cytarabine, and melphalan or carmustine, etoposide, cytarabine, and cyclophosphamide. This pre-conditioning aimed to optimize the transplantation environment. Subsequently, granulocyte colony-stimulating factor was administered to mobilize stem cells. The screening process involved monitoring cluster of differentiation 34-positive (CD34+) hematopoietic stem cells in peripheral blood using flow cytometry. The ideal threshold for peripheral blood CD34+ cells was set at ≥ 20 cells/ μ L. This monitoring enabled prediction of the required collection quantity and duration, with a minimum standard of CD34+ cells not at 2×10^6 /kg. A desirable transplant condition was generally achieved when the final collection of CD34+ cells exceeded 5×10^6 /kg.

Response assessment

Therapeutic response was evaluated in accordance with the international PCNSL Collaborative Group guidelines[1]. Response to treatment was assessed using magnetic resonance imaging and CSF evaluation every second cycle. In accordance with the guidelines, each patient's best response to treatment was recorded to evaluate the ORR, including complete response (CR, no contrast enhancement on imaging) and partial response ($\geq 50\%$ decrease disease enhancement on imaging). Any new lesions were defined as progressive disease (PD), and any other conditions were defined as stable disease. Progression-free survival (PFS) was calculated from the start of treatment to the time of disease progression or death due to PCNSL. Overall survival (OS) was calculated from the date of diagnosis to the time of death from any cause.

Sample collection and processing

CSF and peripheral blood samples were collected and stored at -80°C . Tumor biopsy specimens were obtained using formalin-fixed, paraffin-embedded tissues. Samples were analyzed using capture-based targeted next-generation sequencing in a central testing laboratory (Nanjing Geneseq Technology, Inc., Nanjing, China). This approach, as previously outlined, targets 102 lymphoma-associated genes, facilitating precise genetic characterization[20,21]. The DLBCL [non-germinal center B-cell (non-GCB) or germinal center B-cell (GCB)] subtype was determined using immunohistochemical staining in accordance with the Hans classification, in the Department of Pathology of the Guangdong People's Hospital, Guangzhou, China.

Statistical analysis

GraphPad Prism 9 (version 9.0.2; GraphPad Software, Inc., San Diego, CA, United States) was used for the data analysis. Baseline characteristics were described using medians for continuous variables and percentages for categorical variables. PFS and OS were analyzed by the Kaplan-Meier method, *P* values were calculated using the log-rank test, and *P* < 0.05 indicated a significant difference.

RESULTS

Baseline patients' data

Data for 19 patients with newly diagnosed PCNSL who were treated with HD-MTX plus zanubrutinib were retrospectively analyzed ([Figure 1](#)). The patients' clinicopathological characteristics are summarized in [Table 1](#). The patients' median age was 57 years (range, 27-81 years), and five patients had an Eastern Cooperative Oncology Group performance score > 2 ([Table 1](#)). Ten patients were women, and 16 patients had lesions in deep areas, namely the periventricular tissue, corpus callosum, brainstem, basal ganglia, and/or cerebellum. Eleven patients had high CSF protein concentrations (> 450 mg/L), and only one patient had a high lactate dehydrogenase serum level (> 250 U/L). The International Extranodal Lymphoma Study Group risk score was low-grade in 3 patients, median-grade in 12 patients, and high-grade in 1 patient.

Table 1 Baseline data of the patients with primary central nervous system lymphoma

Characteristic	N = 19
Age, yr	57 (27–81)
Sex, n (%)	
Male	9 (47.4)
Female	10 (52.6)
ECOG-PS ≥ 2 , n (%)	5 (26.3)
Invasion of deep intracranial areas, n (%)	16 (84.2)
High CSF protein concentration (> 450 mg/L), n (%)	11 (68.75) ¹
High LDH serum concentration (> 250 U/L), n (%)	1 (5.3)
IELSG risk score, n (%)	
Low	3 (18.75) ¹
Intermediate	12 (75) ¹
High	1 (6.25) ¹
Follow-up time (mo)	14.7 (3.9–30)

¹Three patients refused lumbar puncture for personal reasons.

ECOG-PS: Eastern Cooperative Oncology Group performance score; CSF: Cerebrospinal fluid; LDH: Lactate dehydrogenase; IELSG: International Extranodal Lymphoma Study Group.

Treatment duration and response

All 19 patients received 120 doses of induction therapy. ASCT was administered as consolidation therapy in nine patients. None of the patients received corticosteroid therapy. HD-MTX therapy was discontinued in one patient due to delayed HD-MTX excretion. Nine patients completed ASCT, with an ORR of 88.9% (CR/PR: 6/2). Eight patients were still in remission at the time of writing (Figure 2 and Table 2). Ten patients received maintenance therapy comprising zanubrutinib with lenalidomide for 6 mo, and zanubrutinib monotherapy was administered continuously until disease progression.

The median follow-up duration was 14.7 mo (range, 3.9–30 mo). All patients were evaluated for treatment response, which revealed CR in 11 patients, partial response in 5 patients, and PD in 3 patients. The ORR was 84.2%, and 2-year PFS and OS rates were 75.6% and 94.1%, respectively. The median PFS and median OS for the entire cohort were not reached (Table 3 and Figure 3).

Safety and adverse events

The prevalent hematological toxicity in patients who received HD-MTX plus zanubrutinib treatment was anemia (100%), followed by lymphocytopenia (84.2%). The leading non-hematological toxicities were hypoalbuminemia (94.7%) and hypokalemia (78.9%) (Table 4). It is noteworthy that no grade 4 non-hematological toxicities were recorded, and the observed adverse effects of therapy were mild and required no additional therapeutic interventions. No treatment-related fatalities were observed.

Clinical response and baseline tumor genomic characteristics

We also explored the association between treatment response and tumor genomic traits. CSF samples were available for eight patients, while six patients had baseline tumor biopsy samples available for genomic analysis (Figure 4). Forty-two genetic alterations were detected (tumor tissue samples: $n = 30$, CSF samples: $n = 30$), and 18 alterations were the same in the primary tumor tissue and CSF samples (Figure 5). The most common mutation detected in both CSF and primary tumor samples was PIM1, followed by alterations of B-cell lymphoma 6, MYD88, GNA13, and TBL1XR1.

Among the 19 patients, 9 had non-GCB disease, with 6 (66.7%) responding positively to the zanubrutinib-based regimen. The remaining 10 patients with GCB disease achieved a 100% response rate to the same regimen. Among the patients with MYD88 alterations, four achieved CR, constituting 50% of this subgroup, with the zanubrutinib-based regimen. In the subset of eight patients with alterations in key genes involved in the BCR pathway, such as CD79B and MYD88, the ORR reached 60%. The response rates for patients with alterations in MYD88 and CD79B were 50% (4/8) and 37.5% (3/8), respectively (Table 2). Two patients (P1 and P7) with alterations in both MYD88 and CD79B genes demonstrated a 50% ORR, with one achieving a CR, as shown in Table 2.

The role of CSF ctDNA in disease surveillance

Eight CSF samples were collected during various treatment cycles, *i.e.*, at baseline and just before cycles 3, 5, and 6. One exception was patient 6, who underwent assessments only after cycle 3 and cycle 6 for personal reasons. Six patients

Table 2 Baseline tumor genomic characteristics of the patients with primary central nervous system lymphoma

Patient	ID	COO Subtype	Best response (mo)	MYD8B	CD79B	Ki-67	Cyclin D1	Other IHC results
p973624	1	Non-GCB	CR (22.2) ¹	L265P	Y196D	> 90%+	NA	CD20(+++), CD79a(+++), CD3(-), CD5(-), CD21(-), CD23(-), Bcl6(>90%+), MUM1(>90%+), FOXP1(>90%+), Bcl2(60%+), c-Myc(40%+), CD30(-), ALK(ALK1)(-), CD138(-), P53(+), c-Met(-), PD-L1(22C3)(30%+)
p968283	2	GCB	CR (23) ¹	NA	NA	100%+	-	CD43(-), CD20(+++), CD3(-), CD79a(+++), CD5(-), CD23(-), CD10(95%+), CD21(-), CD30(-), ALK(ALK1)(-), Bcl6(90%+), CD138(-), MUM1(65%+), Bcl2(50%+), c-Myc(20%+), GFAP(-), Olig2(-)
p955842	3	Non-GCB	SD (6.0)	NA	NA	70%+	-	LCA(+++), OCT-2(+++), CD20(+++), CD19(+++), CD10(-), Bcl6(70%+), MUM1(40%+), CD3(-), CD5(+), ALK(ALK1)(-), CD23(-), CD21(-), CD30(-), CD138(-), Bcl2(++), TdT(-), GECT1(+), FOXP1(+++), c-Myc(80%+), c-Met(-), P53(+++), GFAP(-), CK(-), EMA(-)
p241574	4	Non-GCB	CR (27.5) ¹	NA	K159Q, V223R	90%+	-	LCA(++), CD79a(++), CD43(-), CD20(+), CD3(-), CD5(-), CD23(-), CD10(-), CD21(-), CD30(-), ALK(ALK1)(-), Bcl6(90%+), CD138(-), MUM1(70%+), Bcl2(50%+), TdT(-), GECT1(30%+), FOXP1(+), c-Myc(70%+), c-Met(+), LMP-1(-), EBNA2(-), P53(+), PD-L1(22C3)(90%+)
p939668	5	Non-GCB	PR (28.5) ¹	NA	NA	NA	NA	NA
p932230	6	GCB	CR (29.5) ¹	S219C	NA	98%+	NA	CD20(+++), CD79a(+++), CD3(-), CD5(-), ALK(ALK1)(-), CD21(-), CD23(-), Bcl6(90%+), MUM1(20%+), CD10(100%+), CK(-), Vimentin(-), EMA(-), S100(-), GFAP(-), Bcl2(80%+), GECT1(35%+), FOXP1(80%+), c-Myc(45%+), C-MET(50%+), P53(4%+), PD-L1(22C3)(10%+)
p929763	7	Non-GCB	CR (18.8)	L265P	C.553-2A>C	90%+	-	CD43(-), CD20(+++), CD3(-), CD79a(+++), CD5(-), CD23(-), CD10(-), CD19(+++), CD22(++), CD21(-), CD30(-), ALK(ALK1)(-), Bcl6(10%+), CD138(-), MUM1(20%+), Bcl2(70%+), TdT(-), c-Myc(5%+), GFAP(-)
p173185	8	Non-GCB	PR (8.0)	L265P	NA	NA	NA	ERCC1(-), β -tubulin(+++), EGFR(+++), VEGF(+), ALK(-), CD56(-), CgA(-), Syn(-)
p651739	9	GCB	CR (23.0)	NA	NA	90%+	-	CD43(+), CD20(+++), CD3(+), CD79a(++), CD5(-), CD23(-), CD10(+++), CD21(-), CD30(-), ALK(ALK1)(-), Bcl6(60%+), CD138(-), MUM1(++), Bcl2(-), TdT(-), c-Myc(20%+), GFAP(-), Olig2(-)
p1013138	10	GCB	CR (12.5)	NA	NA	90%+	-	CD3(-), CD5(-), CD20(++), CD79a(++), CD30(-), ALK(ALK1)(-), SALL4(-), OCT3/4(-), AFP(-), GFAP(-), Olig2(-), MUM1(+), CD10(++), Bcl6(++), CD23(-), Bcl2(-), GCET-1(+), FOXP1(+), c-Myc(70%+), c-Met(-), P53(95%+), PD-L1(22C3)(TC <1%+, IC 70%+)
p2010722	11	Non-GCB	PR (16.6)	NA	NA	80%+	-	CK(-), CD20 and CD79a(+), CD3(-), CD5(-), Bcl-2(80%+),

p998505	12	Non-GCB	PR (22.2)	NA	NA	70%+	2%+	MUM-1(+), CD10(-), Bcl6(-) D3(+), CD5(++), CD20(+++), CD79a(+++), CD30(-), CD10(-), GFAP(-), Olig2(-), CK(-), CD43(++), CD23(-), CD21(-), ALK(ALK1)(-), Bcl6(20%+), CD138(-), MUM1(80%+), Bcl2(90%+++), TdT(-), GECT-1(-), FOXP1(+++), c-Myc(70%+), c-Met(-), P53(1%+), PD-L1(22C3)(70%+)
p1013897	13	GCB	CR (14.2)	NA	NA	85%+	-	CD20(+++), CD3(-), CD79a(+++), CD5(-), CD30(<1%+), ALK(ALK1)(-), CD23(-), CD10(+++), CD21(-), Bcl6(70%+), CD138(+), MUM1(40%+), Bcl2(5%+), TdT(-), Cyclin D1(-), c-Myc(40%+), c-Met(60%+), P53(70%+), PD-L1(22C3)(40%+)
p2020811	14	GCB	CR (10.8)	NA	NA	90%+	NA	CD3(+), CD5(+), CD79a(+), CD10(+), Bcl6(±), CD20(+++), Bcl6(80%+), MUM1(<5%+), CD10(+), Ki67(90%+), CD3(-), AE1/AE3(-), EMA(-), P40(-), CD3(-), GFAP(-)
P2003851	15	GCB	CR (13.1)	NA	NA	80%+	-	EMA(-), S100(-), GFAP(+), Syn(+), CgA(-), Olig2(+), NeuN(+), CD34(+), CD3(+), CD5(+), CD79a(+), CD20(+), CD43(10%+), CD30(-), ALK(ALK1)(-), Bcl6(>90%+), Bcl2(90%+), TdT(-), GECT-1(90%+), FOXP1(>90%+), c-Myc(40%+), c-Met(-), LMP-1(-), EBNA2(-), P53(60%+), PD(-), L1(22C3)(30%+)
p996213	16	GCB	CR (18.3)	NA	NA	NA	NA	NA
P1010986	17	GCB	CR (14.7)	NA	NA	95%+	-	CD43(+), CD20(+++), CD3(-), CD79a(++), CD5(-), CD23(-), CD10(60%+), CD21(-), CD30(-), ALK(ALK1)(-), Bcl6(60%+), CD138(-), MUM1(90%+), Bcl2(15%+), TdT(-), c-Myc(30%+)
P2052819	18	Non-GCB	PR (3.9)	NA	NA	90%+	-	GFAP(-), Olig2(-), CD20(+++), CD79a(++), CD3(-), CD5(-), CD21(-), CD23(-), CD10(-), Bcl6(60%+), MUM1(90%+++), CD138(-), Bcl2(90%+++), c-Myc(70%+), CD30(-), ALK(ALK1)(-)
P2045773	19	GCB	PR (5.2)	NA	NA	90%+	-	CD19(+++), CD20(+++), CD3(-), CD5(-), GFAP(-), Olig2(-), CD23(+), CD10(-), CD21(-), CD30(-), ALK(ALK1)(-), Bcl6(70%+), CD138(-), MUM1(70%+), Bcl-2(95%+), TdT(-), c-Myc(40%+), c-Met(-)

¹Still in remission.

PCNSL: Primary central nervous system lymphoma; ID: Identification number; COO: Cell of origin; NA: Not available; IHC: Immunohistochemistry; GCB: Germinal center B cell; CR: Complete response; SD: Stable disease; PR: Partial response; CD: Cluster of differentiation; Bcl6: B cell lymphoma 6; MUM-1: Multiple myeloma antigen 1; FOXP1: Forkhead box protein P1; Bcl2: B cell lymphoma 2; ALK: Anaplastic lymphoma kinase; PD-L1: Programmed death-ligand 1; GFAP: Glial fibrillary acidic protein; LCA: Leucocyte common antigen; TdT: Terminal deoxynucleotidyl transferase; GECT: Gene expression in developing tissues with micro computed tomography; CK: Cytokeratin; EMA: Epithelial membrane antigen; LMP-1: Epstein-Barr virus-encoded latent membrane protein 1; EBNA2: Epstein-Barr virus nuclear antigen 2; P53: Tumor protein 53; EGFR: Epidermal growth factor receptor; VEGF: Vascular endothelial growth factor; CgA: Chromogranin A; Syn: Syndecan; SALL4: Sal-like protein 4; AFP: Alpha fetoprotein; Olig2: Oligodendrocyte lineage transcription factor 2; TC: Tumor cells; IC: Immune cells; D3: Cyclin D3; NeuN: Neuronal nuclear antigen.

showed a robust radiographic response to treatment, resulting in a significant reduction in CSF mutant allele frequency. One patient (P3) showed a stable radiographic response, confirmed by magnetic resonance imaging, but the ctDNA levels remained unchanged in the CSF specimen (Figure 6). However, this patient experienced PD following completion of the zanubrutinib-based induction regimen. Therefore, whole-brain radiotherapy (30 GY) with temozolomide and zanubrutinib was initiated. This approach led to a favorable radiographic response, and the patient is presently

Table 3 Efficacy of high-dose methotrexate plus zanubrutinib for newly diagnosed primary central nervous system lymphoma

Parameter	N = 19
OS rate (%)	-
24-mo (95%CI)	94.1% (83.6%-100%)
Median PFS	-
24-mo (95%CI)	75.6% (53.4%-100%)
ORR (%)	84.2%
ASCT (consolidation therapy)	88.9%
Zanubrutinib (maintenance therapy)	80%
Median follow-up time (mo)	14.7
95%CI	3.9-30

OS: Overall survival; CI: Confidence interval; PFS: Progression-free survival; ORR: Objective response rate; ASCT: Autologous stem cell transplantation.

Table 4 Adverse events in patients treated with high-dose methotrexate plus zanubrutinib

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Total (%)
Hematological toxicities					
Leukopenia	3	7	1		11 (57.9)
Neutropenia	3	6	2		11 (57.9)
Lymphocytopenia	6	8	2		16 (84.2)
Thrombocytopenia	5			1	6 (31.6)
Anemia	8	10	1		19 (100)
Non-hematological toxicities					
Transaminase increase	4				4 (21.1)
Creatinine increase	2	1			3 (15.8)
Hypoalbuminemia	16	2			18 (94.7)
Hypokalemia	10	4	1		15 (78.9)
Lung infection					NA

NA: Not applicable.

continuing with this treatment. Another patient (P8) demonstrated a partial radiographic response. The mutant allele frequency in the CSF decreased markedly with treatment, excluding the gene fusion of BCR-ABL1 (Figure 6). However, this patient developed PD as peripheral lesions, and subsequently received rituximab, zanubrutinib, and lenalidomide (IR2) as second-line treatment.

DISCUSSION

The outcomes in our case series showed that combined therapy with zanubrutinib and HD-MTX was well-tolerated as a frontline therapeutic regimen for patients diagnosed with PCNSL. Nine patients transitioned to ASCT following the zanubrutinib and HD-MTX induction phase, while another 10 patients underwent maintenance therapy with zanubrutinib alone. Only three patients developed disease progression. Data for all 19 patients were included in the evaluation of PFS and OS. Only one patient (P6) discontinued HD-MTX therapy, owing to delayed HD-MTX excretion, and the regimen was changed to rituximab, zanubrutinib, and lenalidomide. No instances of treatment-related mortality were recorded throughout the study. However, limitations exist in our study. It is well recognized that the journey from the initiation of the oncogenic event to the point of clinical diagnosis is protracted, spanning approximately a decade. This extended timeline underscores the intricacies inherent in the development of neoplastic disorders, revealing that the characterization of “newly diagnosed” necessitates a more nuanced understanding—one that acknowledges the substantial

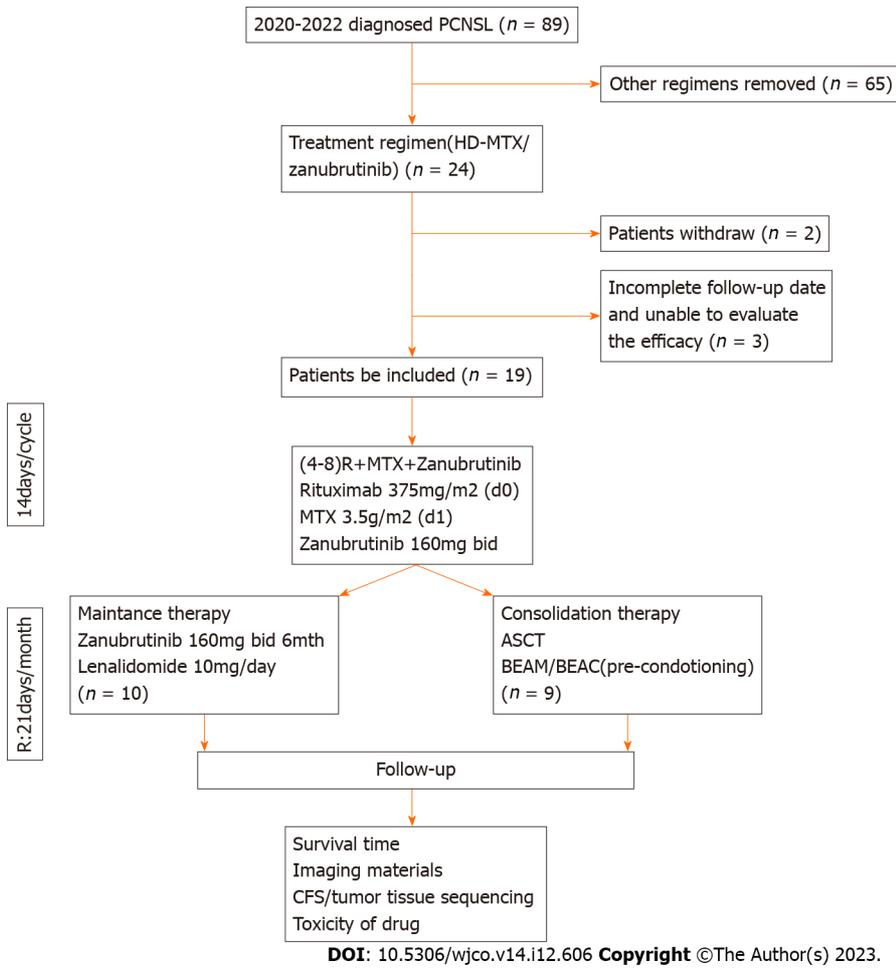


Figure 1 Patient acquisition flow diagram. PCNSL: Primary central nervous system lymphoma; HD-MTX: High-dose methotrexate; ASCT: Autologous stem cell transplantation; BEAM: Carmustine, etoposide, cytarabine, and melphalan; BEAC: Carmustine, etoposide, cytarabine, and cyclophosphamide; CFS: Cancer Fatigue Scale. R:21 days/month: Lenalidomide for maintenance therapy.

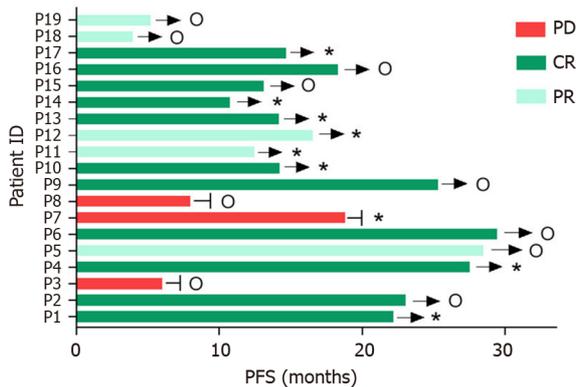
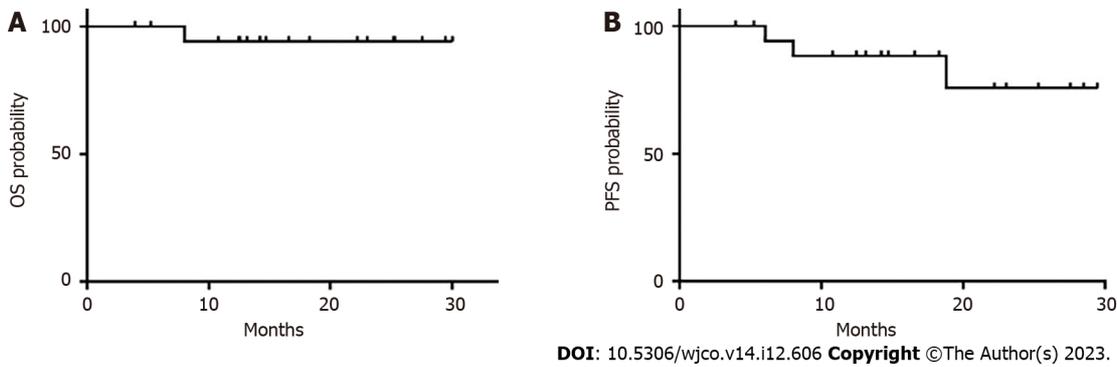


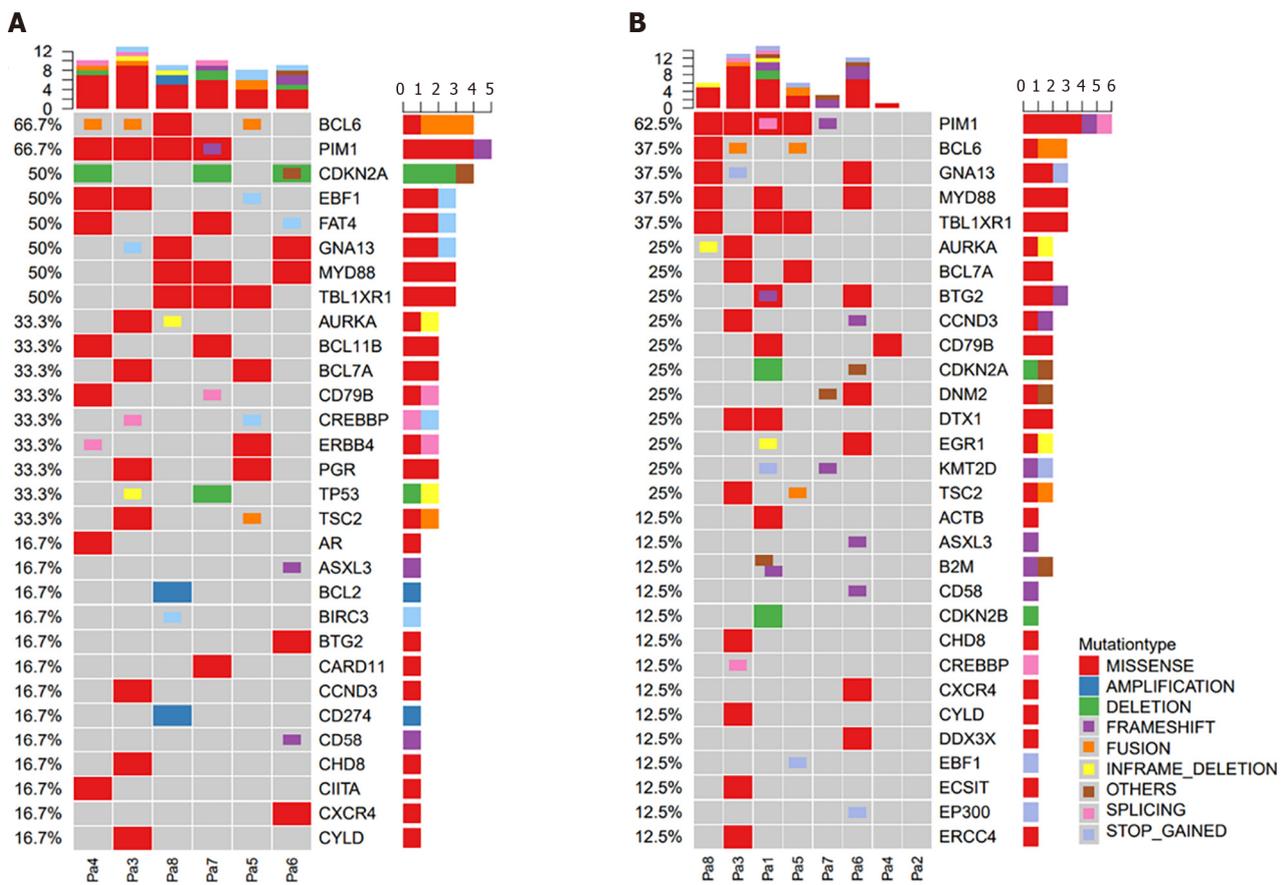
Figure 2 Clinical response and progression-free survival of all patients. o: using a zanubrutinib-based maintenance regimen; *: Using ASCT as a consolidation regimen; →: Ongoing; ||: PD; ID: Identification number; PD: Progressive disease; CR: Complete response; PR: Partial response; PFS: Progression-free survival; ASCT: Autologous stem cell transplantation.

span of disease evolution prior to medical recognition. Our study emphasizes the importance of adopting novel therapeutic strategies to address the multifaceted nature of PCNSL. Historically, HD-MTX has played a pivotal role, serving as a cornerstone for first-line induction regimens in PCNSL. This is owing to its ability to penetrate the blood-brain barrier and achieve effective anti-tumor concentrations [22-24]. However, even with this treatment, approximately half of the patients experience relapse, and 5-year survival rates remain discouragingly low, at 30%-40% [3]. Studies have shown that HD-MTX-based first-line regimens result in an



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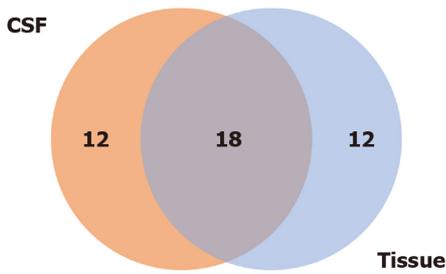
Figure 3 Kaplan-Meier curve for overall survival and progression-free survival. A: overall survival; B: progression-free survival. OS: Overall survival; PFS: Progression-free survival.



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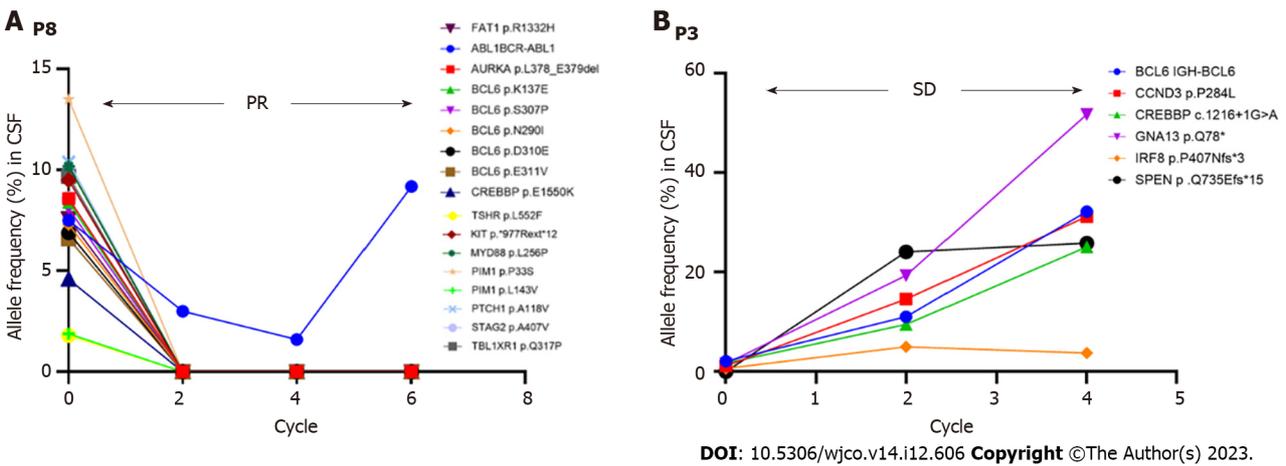
Figure 4 Gene alterations detected in tumor tissue and cerebrospinal fluid. A: Tumor tissue; B: Cerebrospinal fluid. CSF: Cerebrospinal fluid; P: Patient.

ORR of approximately 68% in PCNSL patients over the age of 60 years. In newly diagnosed PCNSL, the median PFS is 35 mo and 8 mo for patients younger and older than 60 years, respectively[22,25]. In this study, the combination of zanubrutinib with HD-MTX demonstrated robust anti-tumor activity, with an ORR of 84.2%, which is higher than that achieved by HD-MTX-based chemotherapy alone. Our results also identified a 2-year PFS of 75.6% and an OS of 94.1%. The median PFS and median OS for the entire cohort were not reached at the time of writing, even after a follow-up of 14.7 mo (range: 3.9-30 mo). Previous studies have shown that zanubrutinib exhibits greater selectivity in inhibiting BTK compared with the off-target effects observed with ibrutinib[26]. The profound BTK inhibition observed with zanubrutinib in both blood and lymph nodes is hypothesized to maximize the potential for deep and sustained remissions in conditions such as chronic lymphocytic leukemia and other hematological disorders. In the phase I BGB-3111-AU-003 study, which evaluated zanubrutinib monotherapy for chronic lymphocytic leukemia/small lymphocytic leukemia, efficacy was assessed in a cohort of 78 patients. This patient group included individuals with high-risk disease features, such as adverse cytogenetics (del(11q), 23.3%; del(17p) and/or TP53 mutation) at a rate of 19.1%[26]. After a



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Figure 5 Concordance between baseline primary tumor tissue and cerebrospinal fluid samples for mutation detection. CSF: Cerebrospinal fluid.



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Figure 6 Disease monitoring during therapy by evaluating cerebrospinal fluid circulating tumor DNA. A: P8; B: P3. PR: Partial response; SD: Stable disease; P8: Patient 8; P3: Patient 3.

median follow-up of 13.7 mo (range: 0.4-30.5 mo), the ORR was 96.2% (75/78) (95% confidence interval: 89.2-99.2). This ORR group included two patients (2.6%) who achieved CR, 63 (80.8%) who achieved PR, and 10 (12.8%) with PR with lymphocytosis[26].

In our study, nine patients completed ASCT after the induction phase of zanubrutinib-based combination therapy and achieved an ORR of 88.9% (CR/PR: 6/2), indicating the advantage of ASCT as a consolidation regimen. Furthermore, studies have shown that ASCT is an effective consolidation strategy in PCNSL[27,28]. Therefore, ASCT should be the first choice for suitable patients.

Lenalidomide is an immunomodulatory agent that shows good anti-tumor activity as a BTK inhibitor in DLBCL[27]. Lenalidomide combined with ibrutinib and rituximab shows promising anti-tumor activity in relapsed/refractory DLBCL[29]. In our study, one patient (P6) achieved CR after receiving an IR2-based regimen and zanubrutinib maintenance. In patients who do not tolerate HD-MTX and experience toxicity, IR2 may be a better choice. In our study, 8 of 10 patients achieved a therapeutic response with zanubrutinib maintenance. Therefore, for PCNSL patients who are unsuitable for ASCT, lenalidomide and zanubrutinib as maintenance therapy might be promising.

PCNSL patients are divided into three major molecular subtypes: A GCB subtype, an activated B-cell (ABC) subtype, and a type III subtype, whose cell origin is unidentified. The first two subtypes account for approximately 80% of all cases; ABC DLBCL patients have poorer outcomes[30]. To our knowledge, there are no reports of the results of zanubrutinib therapy for the GCB and ABC subtypes of PCNSL. Nine of the 19 patients in our study had non-GCB disease and 6 (66.7%) responded to the zanubrutinib-based regimen. Ten patients had GCB disease, and all (100%) responded to the zanubrutinib-based regimen. Zanubrutinib may have had a better effect on the ABC subtype in previous studies.

Previous studies have shown that next-generation sequencing may be used as a molecular diagnostic method prior to delivering targeted therapies, particularly BCR inhibitors, in the case of MYD88-mutated tumors[31]. In our study, CSF liquid biopsies were evaluated using next-generation sequencing in eight patients, while XX underwent radiological evaluation. Six patients had dramatically lower CSF mutant allele frequencies compared with patients 3 and 8. Patient 8 achieved a partial radiographic response during the induction treatment, while the CSF mutant allele frequency increased after cycle 4 (Figure 6). This patient developed PD while receiving the maintenance regimen. As shown in Figure 6, patient 3 had a stable radiographic response, with an increased level of ctDNA in the CSF specimen. This patient developed PD after completing the induction regimen.

Performing CSF liquid biopsy profiling with radiologic evaluation is feasible in PCNSL. Studies show frequent MYD88 and CD79B mutations in PCNSL[6,10-13]. On the basis of the genetic analysis of CSF in our study, we found frequent alterations of MYD88 and CD79B involved in the BCR pathway, and zanubrutinib combined with HD-MTX resulted in good anti-tumor activity. Therefore, CSF liquid biopsy profiling might be feasible for evaluating the response to a therapeutic protocol. However, the fleeting presence of ctDNA in the bloodstream poses a challenge to the reliability of the results of CSF liquid biopsy profiling[32].

An extensive safety analysis performed on pooled data from six zanubrutinib monotherapy trials revealed a notable trend toward favorable tolerability among patients diagnosed with various B-cell malignancies[29]. These conditions, which are often associated with symptoms such as diarrhea, thrombocytopenia, bleeding, atrial fibrillation, skin rash, and fatigue, respond well to zanubrutinib treatment[33]. The results of our study highlight the reassuring absence of grade 4 non-hematological toxicities. The reported side effects were characterized as mild and did not require further therapeutic intervention. No treatment-related mortality was observed, indicating a moderate safety profile for zanubrutinib combined with HD-MTX for patients with PCNSL.

While our findings provide valuable insights into the tolerability of zanubrutinib, this study has limitations. First, owing to the retrospective design and the small number of included patients, larger-scale prospective cohort studies and longer follow-up may be warranted to validate our results. Second, generally, regarding cellular origin in PCNSL, zanubrutinib may have a better effect on the ABC subtype. However, in this study, we were able to identify only the GCB and non-GCB phenotypes owing to the limited experimental conditions; ABC genotyping was not performed. Therefore, it is not possible to conduct a more detailed analysis.

CONCLUSION

Zanubrutinib combined with HD-MTX provided a good clinical response and was well tolerated in newly diagnosed PCNSL patients. Additionally, the detection of ctDNA in CSF was very useful in disease surveillance and treatment response monitoring. However, given the small sample size and retrospective study design, further research is required to validate our findings.

ARTICLE HIGHLIGHTS

Research background

Primary central nervous system lymphoma (PCNSL) is an aggressive brain lymphoma with limited treatment options. The current standard treatment involves high-dose methotrexate (HD-MTX), but there is a need for effective combination therapies to address adverse reactions. Zanubrutinib, a Bruton's tyrosine kinase inhibitor, shows promise owing to its potential to modulate B-cell receptor and Toll-like receptor signaling, which are associated with PCNSL.

Research motivation

This study aimed to evaluate the efficacy and safety of combining zanubrutinib with HD-MTX for newly diagnosed PCNSL patients. Additionally, the study explored the use of circulating tumor DNA (ctDNA) in cerebrospinal fluid (CSF) as a monitoring tool for treatment response.

Research objectives

The main objectives were to assess the treatment outcomes, adverse events, and genomic characteristics of PCNSL patients treated with HD-MTX and zanubrutinib combination therapy, and to investigate the potential of CSF ctDNA in disease surveillance.

Research methods

Nineteen eligible PCNSL patients were included in the study and received HD-MTX and zanubrutinib combination therapy. Clinical responses were evaluated, and ctDNA in CSF was analyzed using next-generation sequencing. Safety, treatment duration, and response were assessed.

Research results

The study demonstrated an overall response rate of 84.2% with the combination therapy, including complete and partial responses. Adverse events were mild and manageable. ctDNA levels in CSF were monitored and correlated with treatment response.

Research conclusions

Zanubrutinib combined with HD-MTX resulted in effective clinical responses in newly diagnosed PCNSL patients. The study highlighted the potential of CSF ctDNA for monitoring treatment response and disease surveillance. This combination therapy demonstrated promising safety and efficacy profiles.

Research perspectives

While the study results are promising, further research with larger patient cohorts and longer follow-up periods is needed to confirm the findings. The potential of zanubrutinib in different molecular subtypes of PCNSL and its long-term effects need to be explored. The clinical use of CSF ctDNA requires further investigation.

FOOTNOTES

Author contributions: The study conception and design were performed by Wang N, Chen FL, and Li WY; Data collection was performed by Wang N; All authors contributed to the data analysis and interpretation; Statistical analysis was performed by Wang N and Chen FL; The first draft of the manuscript was written by Wang N; All authors revised the manuscript.

Institutional review board statement: The study was reviewed and approved by the Guangdong Provincial People's Hospital Institutional Review Board.

Informed consent statement: All patients provided written informed consent to participate in this study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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