World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 March 24; 15(3): 371-374

DOI: 10.5306/wjco.v15.i3.371

ISSN 2218-4333 (online)

EDITORIAL

High-dose methotrexate and zanubrutinib combination therapy for primary central nervous system lymphoma

Budhi Singh Yadav

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Reis F, Brazil

Received: November 23, 2023
Peer-review started: November 23, 2023
First decision: January 12, 2024
Revised: January 13, 2024
Accepted: February 20, 2024
Article in press: February 20, 2024
Published online: March 24, 2024

Budhi Singh Yadav, Department of Radiotherapy & Oncology, Post Graduate Institute of Medical Education & Research, Chandigarh 160012, India

Corresponding author: Budhi Singh Yadav, MD, Professor, Department of Radiotherapy & Oncology, Post Graduate Institute of Medical Education & Research, Regional Cancer Centre, Sector 12, Chandigarh 160012, India. drbudhi@gmail.com

Abstract

In this editorial I comment on the article, published in the current issue of the *World Journal of Clinical Oncology*. Primary central nervous system lymphoma (PCNSL) is a disease of elderly and immunocompromised patients. The authors reported clinical results of 19 patients with PCNSL treated with zanubrutinib/high dose methotrexate (HD-MTX) until disease progression. They demonstrated that the combination of zanubrutinib with HD-MTX led to a marked clinical response and tolerability among these patients. They also observed that cerebrospinal fluid liquid biopsy to detect circulating tumor DNA may be a good option for evaluating treatment response and tumor burden in patients with PCNSL. PCNSL is a challenging disease for treatment as these patients present with different neurological states and comorbidities. Treatment has evolved over the years from whole brain radiotherapy to HD-MTX followed by autologous stem cell transplant. Gradually, treatment of patients with PCNSL is going to become individualized.

Key Words: Primary central nervous system lymphoma; High dose methotrexate; Zanubrutinib; Whole brain radiotherapy; Liquid biopsy

Core Tip: Primary central nervous system lymphoma is treated with high dose methotrexate induction followed by consolidation with whole-brain radiotherapy or autologous stem cell transplant. Depending on the general condition and disease status of these patients they can be offered maintenance therapy. Zanbrutinib may be offered to these patients for maintaining the response to primary treatment.

Citation: Yadav BS. High-dose methotrexate and zanubrutinib combination therapy for primary central nervous system lymphoma. *World J Clin Oncol* 2024; 15(3): 371-374
URL: https://www.wjgnet.com/2218-4333/full/v15/i3/371.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i3.371

INTRODUCTION

This editorial is for the article "Clinical outcomes of newly diagnosed primary central nervous system lymphoma treated with zanubrutinib-based combination therapy" by Wang *et al*[1] in the current issue of *World Journal of Clinical Oncology*. In this study, the authors treated 19 patients with primary central nervous system lymphoma (PCNSL) with zanubrutinib/high dose methotrexate (HD-MTX) until disease progression. They concluded that zanubrutinib in addition with HD-MTX showed a noticeable disease response with a good toxicity profile in these patients. At a median follow-up of 14.7 months (range, 3.9–30 months), the overall response rate (ORR) was 84.2%, and progression-free survival (PFS) and overall survival (OS) rates at 2-year were 75.6% and 94.1%, respectively. They also observed that cerebrospinal fluid (CSF) liquid biopsy to detect circulating tumor DNA (ctDNA) may be a good option for evaluating treatment response and tumor burden in PCNSL. However, considering the limitations of the study such as small sample size, single institutional and retrospective by nature, it may be difficult to draw concrete conclusions from this study.

PCNSL is a relatively rare extranodal non-Hodgkin lymphoma which can manifest in the brain, leptomeninges, spinal cord or eyes. It comprises 3% of all brain malignancies[2]. PCNSL, being a disease of elderly and immunocompromised patients, poses a treatment challenge[3,4]. A few cases have also been reported in immunocompetent patients[5,6]. Age and performance status (PS) are two important prognostic factors which help in deciding the treatment strategy for these patients. Other factors such as comorbidity and organ functions also affect treatment decisions. Usually, 60 years is considered as a cutoff for young *vs* elderly patients; however, this cutoff has fluctuated between 60 to 75 years.

Conventional treatment has not improved survival in these patients[7]. In a randomized trial where whole brain radiotherapy (WBRT) was compared to chemotherapy, median PFS in the WBRT arm and the chemotherapy-only arm was 18 and 12 months, respectively (P = 0.14) and median OS was 32 months (95%CI, 26 to 39 months) *vs* 37 months (95%CI, 28 to 47 months), respectively (P = 0.71)[8]. The standard treatment for PCNSL consists of induction with combination chemotherapy followed by consolidation with WBRT or autologous stem cell transplant (ASCT). As treatment options for PCNSL have increased, OS has improved in these patients. Ferreri *et al*[8] concluded that WBRT and ASCT were both viable and effective options as consolidation therapies after HD-MTX chemotherapy for patients with PCNSL aged < 70 years. A landmark multicenter trial by DeAngelis *et al*[9] demonstrated that combination chemotherapy and radiotherapy improved survival as compared to historical reports of radiotherapy alone in patients with PCNSL. They used a higher dose of radiotherapy, 45 Gy/25#/5 wk, which may lead to increased neurotoxicity in these patients. In another multicentre study, Morris *et al*[10] used rituximab, methotrexate, procarbazine, and vincristine in sequence with consolidation reduced-dose WBRT and cytarabine in PCNSL. They demonstrated that this treatment led to high response rates, long-term disease control with minimal neurotoxicity.

HD-MTX has been the backbone of PCNSL treatment. The role of rituximab in PCNSL is controversial because of its poor CSF penetration. Multiple options are being explored to improve outcomes in these patients. Elderly patients with comorbidity are usually treated with HD-MTX and an alkylating agent. In good responders, it has been consolidated with 23.4 Gy in 13 fractions over 2.5 wk. Few elderly patients with good PS and organ functions have an option of high dose therapy followed by ASCT. Unfit patients not suitable for HD-MTX may be candidates for WBRT, which resulted in 2-year PFS of 30%, as reported by Thiel *et al*[7].

Zanubritinib is a second-generation oral Bruton tyrosin kinase (BTK) inhibitor. It has greater tyrosine kinase selectivity than ibrutinib. A twice-daily dose of 160 mg has been shown to completely occupy BTK receptors[11,12]. In patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma, zanubrutinib was associated with significantly better PFS and toxicity profile as compared to ibrutinib[13].

Wang *et al*[1] explored zanubrutinib with HD-MTX in newly diagnosed PCNSL patients. The ORR and PFS were comparable to those reported by Morris *et al*[10] (ORR = 84.2% *vs* 95%, respectively; 2-year PFS = 75.6% *vs* 77%, respectively). Patients in the trial by Wang *et al*[1] were younger as compared to that of by Morris *et al*[10] (median age 50 *vs* 60 years). There were no treatment-related deaths which indicates a moderate safety profile for zanubrutinib in combination with HD-MTX for patients with PCNSL.

ctDNA can be detected in CSF. It can provide diagnostic and prognostic information. It can identify potential therapeutic targets, monitor the tumour response to treatment and identify residual disease. Its level can predict resistance to treatment and help to identify tumour relapse[14]. Wang *et al*[1] demonstrated an ORR of 50%–60% by identifying different gene mutations in PCNL patients. This kind of intervention will help in providing personalized care to these patients. Although CSF analysis is less invasive than surgery, it may not be possible to do lumbar puncture in all the patients because of different medical conditions.

The tumor microenvironment in the PCNSL is different from the extra central nervous system lymphoma which makes it a difficult disease to treat. There are many target receptors in PCNSL apart from B-cell antigen receptor and Toll-like receptor signaling, such as programmed cell death-1 (PD-1)/PD-1 Ligand and immune activation shown by presence of tumor infiltrating lymphocytes. So, targeting one pathway may not be sufficient to treat such a debilitating disease[15,16]. CSF analysis may not provide information about the tumor microenvironment.

CONCLUSION

Zanubrutinib combined with HD-MTX might be an option for patients with PCNSL. However, cost of the treatment remains a concern with this therapy. Other concerns are that it needs to be tested in a large cohort from multiple centers to see whether these results are reproducible.

FOOTNOTES

Author contributions: Yadav BS contributed to concept design, literature review, manuscript writing, revision, final approval.

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

Country/Territory of origin: India

ORCID number: Budhi Singh Yadav 0000-0001-6185-4139.

S-Editor: Li L
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Wang N**, Chen FL, Pan L, Teng Y, Wei XJ, Guo HG, Jiang XM, Huang L, Liu SC, Liang ZL, Li WY. Clinical outcomes of newly diagnosed primary central nervous system lymphoma treated with zanubrutinib-based combination therapy. *World J Clin Oncol* 2023; **14**: 606-619 [PMID: 38179402 DOI: 10.5306/wjco.v14.i12.606]

2 **Ferreri AJM**. Therapy of primary CNS lymphoma: role of intensity, radiation, and novel agents. *Hematology Am Soc Hematol Educ Program* 2017; **2017**: 565-577 [PMID: 29222306 DOI: 10.1182/asheducation-2017.1.565]

3 **Radotra BD**, Parkhi M, Chatterjee D, Yadav BS, Ballari NR, Prakash G, Gupta SK. Clinicopathological features of primary central nervous system diffuse large B cell lymphoma: Experience from a Tertiary Center in North India. *Surg Neurol Int* 2020; **11**: 424 [PMID: 33365186 DOI: 10.25259/SNI_314_2020]

4 **Makhdoomi R**, Nayil K, Rayees A, Kirmani A, Ramzan A, Khalil MB, Dhar A, Besina S, Chanda N, Lone AR, Qadiri S, Maqbool M. Primary CNS lymphoma in immunocompetent: a review of literature and our experience from Kashmir. *Turk Neurosurg* 2011; **21**: 39-47 [PMID: 21294090 DOI: 10.5137/1019-5149.JTN.3100-10.2]

5 **Beraldo GL**, Brito ABC, Delamain MT, Souza CA, Lima CSP, Bonfitto JFL, Queiroz LS, Reis F. Primary infratentorial diffuse large b-cell lymphoma: a challenging diagnosis in an immunocompetent patient. *Rev Assoc Med Bras (1992)* 2019; **65**: 136-140 [PMID: 30892435 DOI: 10.1590/1806-9282.65.2.136]

6 **Yadav BS**, Mahajan R, Sharma SC, Gupta A, Kumar S. Primary central nervous system lymphoma: an experience of a Regional Cancer Center from India. *J Radiat Cancer Res* 2019; **10**: 104-107 [DOI: 10.4103/jrcr.jrcr_15_19]

7 **Thiel E**, Korfel A, Martus P, Kanz L, Griesinger F, Rauch M, Röth A, Hertenstein B, von Toll T, Hundsberger T, Mergenthaler HG, Leithäuser M, Birnbaum T, Fischer L, Jahnke K, Herrlinger U, Plasswilm L, Nägele T, Pietsch T, Bamberg M, Weller M. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. *Lancet Oncol* 2010; **11**: 1036-1047 [PMID: 20970380 DOI: 10.1016/S1470-2045(10)70229-1]

8 **Ferreri AJM**, Cwynarski K, Pulczynski E, Fox CP, Schorb E, La Rosée P, Binder M, Fabbri A, Torri V, Minacapelli E, Falautano M, Ilariucci F, Ambrosetti A, Roth A, Hemmaway C, Johnson P, Linton KM, Pukrop T, Sønderskov Gørløv J, Balzarotti M, Hess G, Keller U, Stilgenbauer S, Panse J, Tucci A, Orsucci L, Pisani F, Levis A, Krause SW, Schmoll HJ, Hertenstein B, Rummel M, Smith J, Pfreundschuh M, Cabras G, Angrilli F, Ponzoni M, Deckert M, Politi LS, Finke J, Reni M, Cavalli F, Zucca E, Illerhaus G; International Extranodal Lymphoma Study Group (IELSG). Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. *Lancet Haematol* 2017; **4**: e510-e523 [PMID: 29054815 DOI: 10.1016/S2352-3026(17)30174-6]

9 **DeAngelis LM**, Seiferheld W, Schold SC, Fisher B, Schultz CJ; Radiation Therapy Oncology Group Study 93-10. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. *J Clin Oncol* 2002; **20**: 4643-4648 [PMID: 12488408 DOI: 10.1200/JCO.2002.11.013]

10 **Morris PG**, Correa DD, Yahalom J, Raizer JJ, Schiff D, Grant B, Grimm S, Lai RK, Reiner AS, Panageas K, Karimi S, Curry R, Shah G, Abrey LE, DeAngelis LM, Omuro A. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J Clin Oncol* 2013; **31**: 3971-3979 [PMID: 24101038 DOI: 10.1200/JCO.2013.50.4910]

11 **Tam CS**, Trotman J, Opat S, Burger JA, Cull G, Gottlieb D, Harrup R, Johnston PB, Marlton P, Munoz J, Seymour JF, Simpson D, Tedeschi A, Elstrom R, Yu Y, Tang Z, Han L, Huang J, Novotny W, Wang L, Roberts AW. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood* 2019; **134**: 851-859 [PMID: 31340982 DOI: 10.1182/blood.2019001160]

12 **Ou YC**, Tang Z, Novotny W, Cohen A, Wang K, Liu L, Gao Y, Sahasranaman S. Rationale for once-daily or twice-daily dosing of zanubrutinib in patients with mantle cell lymphoma. *Leuk Lymphoma* 2021; **62**: 2612-2624 [PMID: 34159878 DOI: 10.1080/10428194.2021.1929961]

13 **Brown JR**, Eichhorst B, Hillmen P, Jurczak W, Kaźmierczak M, Lamanna N, O'Brien SM, Tam CS, Qiu L, Zhou K, Simkovic M, Mayer J, Gillespie-Twardy A, Ferrajoli A, Ganly PS, Weinkove R, Grosicki S, Mital A, Robak T, Osterborg A, Yimer HA, Salmi T, Wang MD, Fu L, Li J, Wu K, Cohen A, Shadman M. Zanubrutinib or Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N Engl J Med* 2023; **388**: 319-332 [PMID: 36511784 DOI: 10.1056/NEJMoa2211582]

14 **Bobillo S**, Crespo M, Escudero L, Mayor R, Raheja P, Carpio C, Rubio-Perez C, Tazón-Vega B, Palacio C, Carabia J, Jiménez I, Nieto JC, Montoro J, Martínez-Ricarte F, Castellvi J, Simó M, Puigdefàbregas L, Abrisqueta P, Bosch F, Seoane J. Cell free circulating tumor DNA in cerebrospinal fluid detects and monitors central nervous system involvement of B-cell lymphomas. *Haematologica* 2021; **106**: 513-521 [PMID: 32079701 DOI: 10.3324/haematol.2019.241208]

15 **Parkhi M**, Chatterjee D, Bal A, Vias P, Yadav BS, Prakash G, Gupta SK, Radotra BD. Prognostic implications of the tumor immune microenvironment and immune checkpoint pathway in primary central nervous system diffuse large B-cell lymphoma in the North Indian population. *APMIS* 2022; **130**: 82-94 [PMID: 34862664 DOI: 10.1111/apm.13195]

16 **Parkhi M**, Chatterjee D, Radotra BD, Bal A, Yadav BS, Tripathi M. Double-hit and double-expressor primary central nervous system lymphoma: Experience from North India of an infrequent but aggressive variant. *Surg Neurol Int* 2023; **14**: 172 [PMID: 37292392 DOI: 10.25259/SNI_307_2023]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com