High dose methotrexate and zanubrutinib combination therapy in Primary central nervous system lymphoma

Zanubrutinib/HD-MTX in PCNSL

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Abstract
In this editorial I comment on the article by Wang et. al., published in the recent issue of the World Journal of Clinical Oncology. Primary central nervous system lymphoma (PCNSL) is the disease of elderly and immunocompromised patients. The authors reported treatment of 19 PCNSL patients with zanubrutinib/ High dose methotrexate (HD-MTX) until disease progression. They demonstrated that the combination of zanubrutinib with HD-MTX lead to a marked clinical response and tolerability among these patients. 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. 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 this is going to become individualized.

Key Words: Primary central nervous system lymphoma; High dose methotrexate; Zanubrutinib; Whole brain radiotherapy; Liquid biopsy
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**Core Tip:** Primary central nervous system lymphoma (PCNSL) is treated with High dose methotrexate (HD-MTX) induction followed by consolidation with whole-brain radiotherapy (WBRT) or autologous stem cell transplant (ASCT). Depending on the general condition and disease status of these patients they can be offered maintenance therapy. Zanubrutinib may be offered to these patients for maintaining the response to primary treatment.

**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 WJCO. In this study the authors treated 19 patients with primary central nervous system lymphoma (PCNSL) with zanubrutinib/HD-MTX until disease progression. They concluded that zanubrutinib in addition with HD-MTX showed a noticeable disease response with good toxicity profile in these patients. At a median follow-up of 14.7 months (range, 3.9–30 months), the overall response rate was 84.2%, and progression-free- 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. But 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 pose a treatment challenge.[^3] A few cases have also been reported in
immunocompetent patients.\textsuperscript{[5,6]} Age and performance status are two most important prognostic factors which help in deciding the treatment strategy in these patients. Other factors such as comorbidity and organ functions also affect treatment decision. Usually, 60 year is considered as a cutoff for young vs elderly patients, but some clinicians fluctuate it between 60 to 75 years.

Conventional treatment has not improved survival in these patients.\textsuperscript{[7]} In a randomized trial where whole brain radiotherapy (WBRT) was compared to chemotherapy, median progression free survival (PFS) and OS in the WBRT arm and the chemotherapy-only arm was 18 months and 12 months ($P = .14$) and \textsuperscript{2}32 months (95\%CI, 26 to 39 months) vs 37 months (95\%CI, 28 to 47 months), respectively ($P = .71$).\textsuperscript{[8]} The standard treatment for PCNSL consists of induction with combination chemotherapy followed by consolidation with WBRT or autologous stem cell transplant (ASCT). Treatment options for PCNSL are increasing so is the survival in these patients. In a study by Ferreri et al.\textsuperscript{[8]} in patients with PCNSL aged $\leq$70 years, they concluded that WBRT and ASCT were both viable and effective options as consolidation therapies after HD-MTX chemotherapy. A landmark multicenter trial by DeAngelis et al.\textsuperscript{[9]} demonstrated that combination of chemotherapy and radiotherapy improved survival as compared to historical reports of radiotherapy alone in patients with PCNSL. They used higher dose of radiotherapy, 45Gy/25#/5 weeks which may lead to increased neurotoxicity in these patients. In another multicentre study Morris et al.\textsuperscript{[10]} used rituximab, methotrexate, procarbazine, and vincristine (R-MPV) in sequence with consolidation reduced-dose WBRT and cytarabine in PCNSL. They demonstrated that this treatment lead to high response rates, long-term disease control with minimum neurotoxicity.

HD-MTX has been the backbone of PCNSL treatment. Role of rituximab in PCNSL is controversial because of its poor CSF penetration. Multiple options are being explored to improve outcome in these patients. Elderly patients with comorbidity are usually treated with HD-MTX and an alkylating agent. In good responders it is consolidated with 23.4 Gy in 13 fractions over 2.5 week. Few elderly patients with good PS and organ
functions have an option of HDT followed by ASCT. Unfit patients not suitable for HD-MTX are candidates for WBRT, which result in 2-year PFS of 30%.\textsuperscript{[7]}

Zanubrutinib 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 the BTK.\textsuperscript{[11,12]} In patients with relapsed or refractory CLL or SLL, zanubrutinib was associated with significantly better PFS and toxicity profile as compared to ibrutinib.\textsuperscript{[13]}

Wang et al\textsuperscript{[11]} explored zanubrutinib with HD-MTX in newly diagnosed PCNSL patients. The response rates and survival in the study by Wang et al\textsuperscript{[11]} are comparable to those reported by Morris et al\textsuperscript{[10]} (ORR 84.2%, and 2-year PFS 75.6% vs. ORR 95% and 2-year PFS, 77%). Patients in the trial by Wang et al\textsuperscript{[11]} were younger as compared to that of by Morris et al\textsuperscript{[10]} (median age 50 years vs. 60 years). There was no treatment-related death which indicate a moderate safety profile for zanubrutinib in combination with HD-MTX for patients with PCNSL.

cT DNA 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.\textsuperscript{[14]} Wang et al\textsuperscript{[11]} 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 CNS lymphoma which makes it a difficult disease to treat. There are many target receptors in PCNSL apart from B-cell antigen receptor (BCR) and Toll-like receptor (TLR) signaling such as programmed cell death-1 (PD-1)/PD-1 Ligand (PD-L) and immune activation shown by presence of tumor infiltrating lymphocytes (TILs). So, targeting one pathway may not be sufficient to treat such a debilitating disease.\textsuperscript{[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 one of the concerns 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.
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