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EDITORIAL

- 360 Leveraging electrochemical sensors to improve efficiency of cancer detection
Fu L, Karimi-Maleh H
- 367 Mechanisms and potential applications of COPS6 in pan-cancer therapy
Wu T, Ji MR, Luo LX
- 371 High-dose methotrexate and zanubrutinib combination therapy for primary central nervous system lymphoma
Yadav BS
- 375 Role of targeting ferroptosis as a component of combination therapy in combating drug resistance in colorectal cancer
Xie XT, Pang QH, Luo LX
- 378 Approaches and challenges in cancer immunotherapy pathways
Kapritsou M

MINIREVIEWS

- 381 Current interventional options for palliative care for patients with advanced-stage cholangiocarcinoma
Makki M, Bentaleb M, Abdulrahman M, Suhood AA, Al Harthi S, Ribeiro Jr MA

ORIGINAL ARTICLE**Retrospective Study**

- 391 Ferroptosis biomarkers predict tumor mutation burden's impact on prognosis in HER2-positive breast cancer
Shi JY, Che X, Wen R, Hou SJ, Xi YJ, Feng YQ, Wang LX, Liu SJ, Lv WH, Zhang YF

Observational Study

- 411 Clinical application of reserved gastric tube in neuroendoscopic endonasal surgery for pituitary tumor
Chen X, Zhang LY, Wang ZF, Zhang Y, Yin YH, Wang XJ

Prospective Study

- 419 Nomogram based on multimodal magnetic resonance combined with B7-H3mRNA for preoperative lymph node prediction in esophagus cancer
Xu YH, Lu P, Gao MC, Wang R, Li YY, Guo RQ, Zhang WS, Song JX

Clinical and Translational Research

- 434** Establishment of a prognosis predictive model for liver cancer based on expression of genes involved in the ubiquitin-proteasome pathway

Li H, Ma YP, Wang HL, Tian CJ, Guo YX, Zhang HB, Liu XM, Liu PF

META-ANALYSIS

- 447** Transarterial chemoembolization plus stent placement for hepatocellular carcinoma with main portal vein tumor thrombosis: A meta-analysis

Sui WF, Li JY, Fu JH

CASE REPORT

- 456** PD-1 antibody in combination with chemotherapy for the treatment of SMARCA4-deficient advanced undifferentiated carcinoma of the duodenum: Two case reports

Shi YN, Zhang XR, Ma WY, Lian J, Liu YF, Li YF, Yang WH

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

Budhi Singh Yadav

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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

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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. Zanubrutinib may be offered to these patients for maintaining the response to primary treatment.

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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].

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 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

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