90490_Auto_Edited.docx

WORD COUNT	1706	TIME SUBMITTED	10-APR-2024 05:07PM
		PAPER ID	108177590

Name of Journal: *World Journal of Clinical Oncology*

Manuscript NO:

Manuscript Type: EDITORIAL

Bruton's tyrosine kinase inhibitors in primary central nervous system lymphoma: New hopes on the horizon

Leonardo S Lino-Silva, Sabrina B Martínez-Villavicencio, Luisa Fernanda Rivera-Moncada

Abstract

In this editorial, we comment on the article by Wang N published in the recent issue of the *World Journal of Clinical Oncology*. This manuscript explores the potential synergistic effects of combining zanubrutinib, a novel oral inhibitor of Bruton's tyrosine kinase, with high-dose methotrexate (HD-MTX) as a therapeutic intervention for primary central nervous system lymphoma (PCNSL). The study involves a retrospective analysis of 19 PCNSL patients, highlighting clinicopathological characteristics, treatment outcomes, and genomic biomarkers. The results indicate the combination's good tolerance and strong antitumor activity, with an 84.2% overall response rate. The authors emphasize the potential of zanubrutinib to modulate key genomic features of PCNSL, particularly mutations in myeloid differentiation primary response 88 and cluster of differentiation 79B. Furthermore, the study investigates the role of circulating tumor DNA in cerebrospinal fluid for disease surveillance and treatment response monitoring. In essence, the study provides valuable insights into the potential of combining zanubrutinib with HD-MTX as a frontline therapeutic regimen for PCNSL. The findings underscore the importance of exploring alternative treatment modalities and monitoring genomic and liquid biopsy markers to optimize patient outcomes. While the findings

suggest promise, the study's limitations should be considered, and further research is needed to establish the clinical relevance of this therapeutic approach for PCNSL.

INTRODUCTION

In this editorial we comment on the article by Wang N published in the recent issue of the *World Journal of Clinical Oncology* [1].

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive subtype of non-Hodgkin lymphoma that primarily affects the central nervous system (CNS), including the brain, spinal cord, and eyes. This malignancy is distinct from systemic lymphomas as it arises and remains confined within the CNS, presenting unique diagnostic and therapeutic challenges. The majority of PCNSL cases are classified as diffuse large B-cell lymphoma (DLBCL), which is often associated with immunocompromised states such as individuals with human immunodeficiency virus/acquired immunodeficiency syndrome or those undergoing immunosuppressive therapy. PCNSL comprises approximately 2%-3% of all primary brain tumors, with an increasing incidence noted in recent years, particularly among the elderly and immunocompromised populations[2]. While the precise etiology remains unclear, immunosuppression, chronic inflammation, and infections such as with the Epstein-Barr virus have been suggested as potential risk factors[3].

PCNSL typically presents with nonspecific neurological symptoms including cognitive decline, focal neurological deficits, and seizure[4]. Ocular involvement, termed primary intraocular lymphoma, may occur concurrently, adding to the complexity of diagnosis[4]. Given the lack of pathognomonic clinical features, the definitive diagnosis often requires brain biopsy, as imaging findings may overlap with other brain lesions[4]. Prognosis in PCNSL is influenced by various factors. Advanced age, immunocompromised status, deep-seated lesions, and elevated lactate dehydrogenase levels at diagnosis are associated with poorer outcomes[5]. Additionally, the blood-brain barrier poses a

challenge by limiting the efficacy of systemic treatments, contributing to the overall difficulty in managing PCNSL.

The primary treatment approach for PCNSL involves a combination of high-dose methotrexate (HD-MTX)-based chemotherapy and, in some cases, radiation therapy[6]. HD-MTX, which crosses the blood-brain barrier, forms the backbone of most treatment regimens. The addition of rituximab, an anti-cluster of differentiation 20 (CD20) monoclonal antibody, to chemotherapy protocols has improved outcomes and is now commonly incorporated into treatment strategies. For eligible patients, consolidation therapies such as autologous stem cell transplantation may be considered[6]. Current research in PCNSL focuses on identifying novel therapeutic strategies to enhance treatment efficacy and reduce toxicity. Immunotherapeutic approaches, including chimeric antigen receptor T-cell therapy, are being investigated for their potential in targeting lymphoma cells within the CNS[7]. Additionally, targeted therapies, such as Bruton's tyrosine kinase (BTK) inhibitors, are under exploration, offering promising avenues for future treatment modalities[8]. PCNSL represents a unique and challenging entity within the spectrum of lymphomas. Advances in diagnostic techniques, treatment modalities, and ongoing research are essential for improving outcomes in patients with this rare malignancy.

BTK INHIBITORS AND LYMPHOMAS

Lymphomas, a heterogeneous group of blood cancers, often exhibit dysregulated signaling pathways that contribute to their pathogenesis. One key target for therapeutic intervention in lymphomas is BTK, a crucial enzyme in B-cell receptor signaling. In recent years, the development of BTK inhibitors has shown remarkable promise in the treatment of various lymphoid malignancies.

In the realm of lymphoma therapeutics, inhibitors targeting BTK have emerged as pivotal agents, with notable contenders including ibrutinib, acalabrutinib, and zanubrutinib.

Ibrutinib, which was granted approval for the treatment of chronic lymphocytic leukemia (CLL) and mantle cell lymphoma, has substantiated its efficacy through rigorous clinical trials[9]. Meanwhile, acalabrutinib, indicated for chronic lymphocytic leukemia and mantle cell lymphoma, has garnered attention for its distinctive selectivity and potency, a topic extensively elucidated in the study by Barf *et al*[10]. On a similar note, anubrutinib, specifically designed for adult mantle cell lymphoma, has undergone scrutiny in a phase 1 trial overseen by Tam *et al*[11], shedding light on both its safety profile and clinical effectiveness. Recent investigations have extended the application of BTK inhibitors to PCNSL. Zanubrutinib, in combination with HD-MTX, has emerged as a promising therapeutic avenue for newly diagnosed PCNSL[1]. A notable aspect of these studies involves the exploration of liquid biopsy techniques, particularly the use of circulating tumor DNA (ctDNA) in cerebrospinal fluid. This innovative approach has been proposed as a potential monitoring tool for treatment response, providing valuable insights into disease surveillance.

Bruton's tyrosine kinase (BTK) is an intracellular tyrosine kinase (non-membrane receptor) composed of 659 amino acids, with its gene located on chromosome Xq21.33-q22. BTK belongs to the tyrosine kinase family known as TEC. The domains that make up the structure of BTK are: a pleckstrin homology (PH) domain in the N-terminal region, which facilitates binding to lipid regions of phosphatidylinositol on the plasma membrane; a Src homology 2 (SH2) domain involved in protein-protein interaction binding to phosphorylated tyrosines; an SH3 domain with binding to proline-rich regions, and a C-terminal catalytic domain.

An important point to note is that pharmacological inhibition of BTK activity not only interferes with signaling through the B-cell receptor (BCR) but also with signals from the tumor microenvironment, such as those induced by chemokines and other survival factors for leukemic cells. Thus, BTK inhibitors promote the egress of the leukemic clone from its survival niches in lymphoid tissues, directing it towards cell death.

BTK inhibitors are classified as reversible or irreversible, depending on the site of inhibition on the protein. Irreversible inhibitors covalently bind to the cysteine residue at amino acid position 481 (kinase activity site), blocking ATP binding; restoration of activity requires synthesis of new protein. Reversible inhibitors bind tightly to BTK but not covalently, resulting in transient ATP blockade. Irreversible or reversible BTK inhibitors potentially bind to other kinases with lower affinity, particularly those of the TEC family. This binding can lead to side effects and specific toxicity profiles, depending on which and how many kinases are inhibited. Therefore, increasing selectivity for BTK reduces the risk of toxicities.

While the progress in BTK inhibition for lymphomas is encouraging, challenges and questions persist. Further research is warranted to validate these findings in larger cohorts, assess long-term effects, and explore the efficacy of BTK inhibitors across molecular subtypes of lymphomas. The continuous trajectory of research in this domain is characterized by a relentless pursuit of optimizing therapeutic efficacy while minimizing adverse effects, underscoring the dynamic nature of this field.

CLINICAL IMPLICATIONS

The study reports an overall response rate of 84.2%, with a 2-year progression-free survival of 75.6% and an overall survival of 94.1%. The safety profile is described, with a focus on hematological and non-hematological toxicities.

The efficacy results against genotoxic therapy are so successful that the end of chemo-immunotherapy in some neoplasms, including lymphoma, especially for CLL, is now a recognized postulate by leading research groups. Importantly, the manuscript explores the role of ctDNA in cerebrospinal fluid for disease surveillance and treatment response monitoring. Changes in ctDNA levels corresponded to radiographic responses in some patients, highlighting the potential utility of liquid biopsy profiling in PCNSL.

The treatments for Primary Central Nervous System Lymphoma (PCNSL) and Diffuse Large B-cell Lymphoma (DLBCL) differ significantly. High-dose methotrexate (HD-MTX)

stands as the primary therapy for PCNSL. Zanubrutinib, a novel oral Bruton's tyrosine kinase (BTK) inhibitor, holds promise as a therapeutic intervention targeting B-cell antigen receptor (BCR) and Toll-like receptor (TLR) signaling pathways. BTKs traverse the blood-brain barrier. This study investigates the oncological outcomes of a combined regimen of methotrexate with zanubrutinib. An advantage of this study is the molecular profiling of tumors, either from paraffin-embedded tissue, peripheral blood, or cerebrospinal fluid. Complete response was achieved in 11 patients, partial response in 5 patients, and disease progression in 3 patients. The Overall Response Rate (ORR) was 84.2%, with a 5-year overall survival of 94.1%, notably better in cases with a germinal center genotype. Perhaps the most significant point of this article is the observed survival rate, which surpasses the estimated rate in the literature for this lymphoma subtype, typically below 30%. The only potential confounder in this series and its results is the median age of patients (57 years), as age over 60 is an adverse prognostic factor in this lymphoma; however, this median age aligns with literature estimates. One should approach these findings with caution due to the retrospective nature of the study, where the selection criteria for the 19 patients treated with zanubrutinib are not precisely defined. Although inclusion and exclusion criteria were established, it remains unclear whether cases were consecutively recruited and the criteria for initiating treatment with zanubrutinib.

The study's findings have future implications, including the necessity for larger-scale prospective cohort studies and longer follow-up periods to validate the results, and the study underscores the potential of zanubrutinib as a frontline therapeutic regimen for PCNSL, paving the way for further research into optimizing treatment strategies.

CONCLUSION

In summary, BTK inhibitors represent a transformative approach within the landscape of treatments for lymphomas. The evolving understanding of their mechanisms, coupled with developments of innovative applications in PCNSL and liquid biopsy monitoring,

signifies a promising era in lymphoma therapeutics. Continued research endeavors are crucial to fully exploit the potential of BTK inhibitors for enhanced patient outcomes.

90490_Auto_Edited.docx

ORIGINALITY REPORT

10%
SIMILARITY INDEX

PRIMARY SOURCES

1	f6publishing.blob.core.windows.net Internet	55 words — 3%
2	Melek Yakar, Durmuş Etiz. "Circulating tumor cells as prognostic marker in pancreatic cancer", World Journal of Clinical Oncology, 2024 Crossref	44 words — 2%
3	link.springer.com Internet	26 words — 1%
4	www.omicsdi.org Internet	24 words — 1%
5	www.frontiersin.org Internet	21 words — 1%
6	Patricia A. Goodman, Carla M. Wood, Alexei O. Vassilev, Chen Mao, Fatih M. Uckun. "Defective Expression of Bruton's Tyrosine Kinase in Acute Lymphoblastic Leukemia", Leukemia & Lymphoma, 2009 Crossref	14 words — 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS