Central nervous system prophylaxis: it's time to start from scratch

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In this issue of *Haematologica*, Tolley and colleagues conducted a systematic review and meta-analysis of studies evaluating the use of prophylactic high-dose methotrexate (HDMTX) with front-line therapy for systemic diffuse large B-cell lymphoma (DLBCL) to reduce the incidence of secondary central nervous system lymphoma (SCNSL).[1] Consistent with other similar meta-analyses and the current body of literature, which is primarily composed of retrospective studies, HDMTX prophylaxis provides minimal to no benefit in high-risk DLBCL.[2]

Despite the authors' rigorous methodology aimed at reducing data duplication and residual bias, and notwithstanding significant heterogeneity across the various cohorts included in this and other studies, the clinical benefit from prophylactic HDMTX is significantly lower than previously anticipated. For over a decade now, HDMTX prophylaxis has been regarded as standard of care for patients with high-risk systemic DLBCL.[3,4] This situation generates a disconnect between expectations and reality, prompting several follow-up questions.

First, how did this situation arise? The concept of central nervous system (CNS) prophylaxis emerged in the 1990s when lymphoid malignancies were classified based on morphology and limited immunophenotyping, and when classic cytotoxic drugs and radiotherapy were the only treatment options available. Regimens for distinct entities with frequent SCNSL involvement, such as acute lymphoblastic leukemia or Burkitt lymphoma, incorporated intrathecal and/or intravenous HDMTX with varying success. This practice was extended to a broader range of aggressive lymphomas with lower SCNSL risk. For example, intrathecal prophylaxis was mandatory in selected high-risk patients with aggressive B-cell lymphomas (approximately 20% would not be classified as DLBCL today) in the RICOVER-60 trial, which began accrual in 2001.[5]

HDMTX became widely available for the treatment of primary and secondary CNS lymphomas in the early 2000s, and as clinicians became comfortable with its delivery and toxicity, its use was extended as an alternative and/or adjunct to intrathecal prophylaxis. Retrospective series of prophylactic HDMTX with rituximab-containing chemotherapy in high-risk DLBCL observed numerically lower rates of SCNSL than previously documented.[2] This level of evidence was deemed sufficient to adopt HDMTX prophylaxis globally, despite the absence of dedicated confirmatory phase II or III studies. As early as 2010, experts recommended HDMTX prophylaxis for high-risk patients,[3] and by 2012, it was already integrated into international clinical practice guidelines.[4]

Second, why was a randomized study never conducted? The obvious phase III design would randomize a population of DLBCL patients with a relatively high risk of SCNSL to receive HDTMX or no prophylaxis. Assuming a 7.1% cumulative 5-year incidence of SCNSL without HDMTX in high-risk patients,[6] and an optimistic hazard ratio of 0.5 associated with HDMTX, with a power of 0.8 and a two-sided α of 0.05, approximately 1,250 patients would need to be randomized. Assuming each patient received two doses of prophylactic HDMTX, approximately 2,500 hospital admissions would be necessary. Such a study would be extremely expensive and resource-intensive for cooperative groups, and of no interest to the pharmaceutical industry. Also, accrual would likely be challenging due to strong physician biases and patient preferences informed by existing data.

Third, could HDMTX be an inadequate prophylactic agent? HDMTX (typically at a dose of 8 g/m^2 for at least 4-6 doses), with or without rituximab, is associated with modest overall and complete responses (approximately 50% and 35%, respectively) as treatment for established CNS lymphomas.[7] In the study by Tolley and colleagues, HMDTX as prophylaxis for SCNSL was given at variable individual doses (range, 1-3.5 g/m^2) for a variable number of total doses (median 2 doses; range, 1-6) at various points during systemic chemoimmunotherapy.[1] Such heterogeneity in therapy regimens,

coupled with reduced intensity of CNS-directed treatment, further dilutes the overall effectiveness of HDMTX.

Even if one accepts HDMTX as an active prophylactic intervention, in the largest retrospective series with 2,418 patients, the 5-year adjusted absolute risk reduction in SCNSL was 1.6%. Therefore, approximately 63 patients would need to be treated with HDMTX to prevent one instance of SCNSL.[6] This suggests that HDMTX has very limited clinical efficacy as prophylaxis.

Fourth, is the concept of prophylaxis flawed? Comprehensive CNS staging at diagnosis with magnetic resonance imaging, cerebrospinal fluid analysis, and ocular slit lamp examination was not consistently performed in any of the prophylaxis studies. This suggests some patients had subclinical CNS involvement missed by staging (or lack thereof), and questions whether they may have been more adequately treated for established SCNSL had this information been known. The presence of cell-free DNA in the cerebrospinal fluid identifies additional patients with negative conventional CNS staging who subsequently develop SCNSL, but more importantly, its absence is associated with a high negative predictive value.[8,9] Further research is required to determine whether this methodology can better refine the population of patients requiring CNS treatment, those who may benefit from prophylaxis, and those for whom CNS-directed therapies are unnecessary.

Lastly, where do we proceed from here? We are no longer in the 1990s. In 2024, we recognize the molecular complexity of DLBCL and have an increasing array of non-cytotoxic therapies with activity in CNS lymphomas, including immunomodulatory drugs, Bruton tyrosine kinase inhibitors, bispecific antibodies, and chimeric antigen receptor T-cell therapy. Studies of these therapies in combination with chemoimmunotherapy in DLBCL will provide valuable data on rates of secondary CNS relapse and may in turn inform the design of dedicated studies on CNS prophylaxis incorporating comprehensive, in-depth CNS assessments that can be efficiently conducted without a traditional phase III design.

With good intentions but lacking a clear understanding of its true benefit, for years we have consented DLBCL patients for prophylactic HDMTX. The study by Tolley and colleagues[1] provides an opportunity to reflect on a practice that was adopted in an era when the threshold to accept therapies as standard of care was much lower than it is today. It is never wrong to recognize that decisions made in the past with information available at the time were retrospectively flawed. But time has passed. Today we have newer diagnostics and therapeutics, opening an opportunity to start from scratch and (hopefully) improve outcomes for patients with high-risk DLBCL.

Disclosures

DV has received honoraria from and sat on advisory boards for AstraZeneca, Janssen, BeiGene, Kite/Gilead, BMS/Celgene, Merck, Abbvie, Roche, and Incyte and has received research funding (to his institution) from Roche and AstraZeneca.

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