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CONTROVERSIES AND CURRENT PRACTICES IN CNS RELAPSE OF DIFFUSE LARGE B-CELL LYMPHOMA

Introduction

Central nervous system (CNS) relapse is an uncommon complication of diffuse large B-cell lymphoma (DLBCL), occurring in approximately 3-5% of patients and at a median timepoint of 6-9 months from diagnosis.[1] Approximately half of these cases present as isolated CNS relapse caused by occult seeding of the CNS early in the disease course, while the remaining cases occur in the context of concurrent systemic relapse.[2] The median survival after CNS relapse is only 4-6 months,[3] highlighting the unmet need to identify effective prophylaxis and management strategies. This article provides an overview of current controversies and optimal strategies for prognosticating, preventing, and treating CNS relapse in patients with DLBCL.

Can CNS relapse be prognosticated?

The most well-established risk model for prognosticating CNS relapse in DLBCL is the CNS-IPI score, which is comprised of the 5 risk factors of the International Prognostic Index (age >60 years, Eastern Cooperative Oncology Group [ECOG] performance status >1, elevated lactate dehydrogenase [LDH], >1 extranodal site, stage III/IV) with the addition of kidney or adrenal involvement[4]. The 12-23% of patients with 4-6 risk factors have a 10-12% incidence of CNS relapse, which is considered to be high risk. Unfortunately, almost half of the patients who experience CNS relapse do not have a high-risk CNS-IPI score at diagnosis, and almost 90% of patients with a high-risk CNS-IPI score do not develop CNS relapse. There is also significant heterogeneity within the high-risk CNS-IPI group, with the CNS relapse risk ranging from 7% for a score of 4 to 32% for a score of 6.[4] Incorporation of the molecular cell-of-origin into the CNS-IPI model may improve prognostic capability, as patients with a high CNS-IPI score and activated B-cell subtype have a 15% risk of CNS relapse.[5] Prior reports have suggested that MYC and BCL2 protein over-expression or gene rearrangements are also associated with >10% risk of CNS relapse.[1] However, a more recent study found that the 2-year cumulative incidence of CNS relapse in patients with *de novo* double hit lymphoma treated with curative intent was only 6% for those with DLBCL morphology and 11% for high grade morphology.[6] In addition, several clinical or anatomic risk factors are associated with a >10-20% risk of CNS relapse, including the presence of multiple extranodal sites, markedly elevated LDH, and testicular, uterine, or breast lymphoma.[1] These risk factors also have limited sensitivity and specificity for prognosticating CNS relapse, and further work is needed to identify a group of patients with DLBCL at uniformly high risk of CNS relapse.

Is there a role for CNS prophylaxis in DLBCL?

CNS prophylaxis remains an area of considerable controversy despite limited evidence of benefit. Interestingly, the only agent proven in a randomized trial to reduce the risk of CNS relapse is rituximab,[7] and the risk of CNS relapse has fallen to 3% in the rituximab era likely owing to improved control of systemic disease.[8] While intrathecal (IT) chemotherapy has been a commonly used prophylactic approach in DLBCL, it does not penetrate the brain parenchyma where the majority of CNS relapses occur. In addition, a systematic review examining 7,357 rituximab/obinutuzumab-exposed patients from 14 studies concluded there is no evidence that IT chemotherapy reduces the risk of CNS relapse in DLBCL.[9]

Intravenous high-dose methotrexate (HD-MTX) does penetrate the blood-brain barrier and has become widely used as a prophylaxis agent in DLBCL. However, it is a resource-intensive therapy that typically requires 4-5 days of hospitalization with careful monitoring and supportive care to prevent toxicities including mucositis, renal or hepatic dysfunction, and myelosuppression. As a result, HD-MTX may not be feasible for many patients, including those with older age or medical comorbidities. Several small studies suggested that HD-MTX prophylaxis may be associated with lower risks of CNS relapse.[10,11,12] However, these studies must be interpreted cautiously given their retrospective design, small sample size, lack of concurrent controls, and/or obvious selection biases such as using HD-MTX only for fit patients who achieved a complete response with R-CHOP. Despite the limited evidence, international guidelines adopted the recommendation that HD-MTX prophylaxis be administered to patients with DLBCL at high risk of CNS relapse.[13,14] Importantly, over the past 2 years, several groups have reported their experience with HD-MTX prophylaxis and consistently concluded that this practice does not appear to reduce the risk of CNS relapse.[15,16,17,18,19] In the largest of these studies which included almost 2,300 high-risk patients, the use of HD-MTX was not associated with a significant reduction in the risk of CNS relapse overall nor in any high-risk subgroup.[18] In a separate retrospective study of 1,384 patients, CNS relapse rates remained as high as 9% despite the uniform administration of HD-MTX prophylaxis, casting further doubt on the efficacy of this intervention.[19] Importantly, the intercalation of HD-MTX between R-CHOP cycles was associated with a 20% risk of R-CHOP treatment delays and a trend to increased treatment-related mortality.[19] This is of particular concern given that patients at risk of CNS relapse are at even greater risk of systemic disease progression, and the safe and timely administration of R-CHOP is paramount.

Taken in totality, the available data is clear that there is no proven role for the routine administration of CNS prophylaxis in DLBCL. A matter of ongoing debate is whether there are any high-risk subgroups who might still benefit from

CNS prophylaxis. For example, a phase II trial of 38 patients with intravascular large B-cell lymphoma found that the combination of R-CHOP and HD-MTX resulted in a CNS relapse risk of 3%, which is remarkably low for this high-risk subtype of DLBCL.[20] Another subgroup with a particularly high risk of CNS relapse are patients with primary testicular lymphoma, for which prophylactic HD-MTX is often recommended based on a phase II trial of 54 patients reporting a 5-year CNS relapse rate of 0%.[21] However, there are insufficient data to definitively confirm a benefit of HD-MTX prophylaxis even in these high-risk subgroups, and the potential risks must be weighed against the lack of proven benefit in discussion with patients. Specifically, if a physician chooses to treat a patient with HD-MTX prophylaxis despite the unproven benefit for any subgroup of patients with DLBCL, then it should be administered after completion of R-CHOP to reduce the risks of toxicity and optimize relative dose intensity of the more important R-CHOP treatment.[19]

How should CNS relapse be treated?

CNS relapse is associated with a poor prognosis and there are no randomized controlled trials to guide management. Conventional chemotherapy with CNS-penetrating drugs such as HD-MTX and cytarabine are frequently used, but most responses tend to be short-lived.[22] As a result, consolidation with thiotepa-based high-dose chemotherapy and autologous stem cell transplantation (ASCT) should be considered based on the durable remissions demonstrated in several prospective studies.[23,24,25] In the phase II MARIETTA trial, 75 patients with secondary CNS lymphoma (SCNSL) received MATRix and R-ICE induction followed by thiotepa/BCNU conditioning and ASCT, yielding a 2-year progression-free survival (PFS) rate of 46% for all patients and 83% among those who received ASCT in an exploratory analysis.[25] In a recently published series from Alberta, the 5-year PFS was 53% for 62 consecutive patients with SCNSL intended for ASCT, and 62% for the 52 patients who received high-dose thiotepa, busulfan, melphalan, rituximab conditioning and ASCT.[26] Of note, the outcomes with ASCT are better for patients with isolated CNS relapse compared to those with concurrent CNS and systemic disease.[26,27]

Alternative treatments are needed for patients who are ineligible for ASCT due to poor medical fitness or chemo-refractory disease. Preliminary evidence suggests that chimeric antigen receptor (CAR) T-cell therapy achieves encouraging response rates in CNS lymphoma with comparable rates of cytokine release syndrome and neurotoxicity as with systemic lymphoma, although larger studies with longer follow-up are needed to confirm the durability of responses.[28] Targeted agents such as Bruton's tyrosine kinase (BTK) inhibitors or lenalidomide also have established activity in CNS lymphoma.[29,30] Palliative whole-brain radiation therapy (WBRT) may also be considered but is associated with risks of neurotoxicity and poor long term survival.[31]

What does the future hold for CNS relapse?

Given the lack of demonstrable benefit and the potential toxicities of HD-MTX, novel CNS prophylaxis strategies are needed. Targeted agents such as the BTK inhibitor ibrutinib or the immunomodulator lenalidomide do penetrate the blood-brain barrier, but neither has been confirmed to be beneficial in DLBCL and no adequately powered studies have been performed to evaluate their role as agents for CNS prophylaxis.[32,33] Surprisingly, a post-hoc analysis of one randomized trial found that maintenance lenalidomide after R-CHOP was associated with increased risks of CNS relapse.[34] More promising strategies under investigation include the incorporation of molecular tumor profiling or cerebrospinal fluid circulating tumor DNA (ctDNA) analysis to identify patients at very high risk of CNS relapse who might benefit from prophylaxis, although confirmation in larger studies is needed.[35,36,37] Finally, it is also hoped that advances in the treatment of DLBCL, including the integration of polatuzumab vedotin into frontline therapy and the use of second-line CAR T-cell therapy, might reduce the risk of CNS relapse by optimizing control of systemic disease.[38,39,40]

Conclusion

While the optimal strategies for prognosticating and preventing CNS relapse remain controversial, there is growing consensus that prophylactic IT chemotherapy and HD-MTX likely provide no significant benefit for most patients with DLBCL. As the field moves beyond the CNS-IPI score to incorporate novel risk stratification tools including genomic subgrouping and high-sensitivity ctDNA analysis, it is possible that selective targeting of CNS prophylaxis to ultra-high-risk subgroups may prove to be a more effective strategy in the future. In the meantime, clinicians can reassure their patients that the risk of CNS relapse remains low in the rituximab era, and it will hopefully continue to decline as novel therapies emerge to improve systemic disease control. In addition, the early detection of CNS involvement and the timely administration of thiotepa-based ASCT is a promising strategy to overcome the historically poor prognosis of CNS relapse.

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