Central nervous system prophylaxis in diffuse large B-cell lymphoma: a race to the bottom

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In this issue of *Haematologica*, Bobillo *et al.* address the controversial topic of chemotherapy as central nervous system (CNS) prophylaxis during front-line management of diffuse large B-cell lymphoma (DLBCL).[1] Despite the fact that CNS spread is a feared and often terminal complication of DLBCL treatment, there is no broad consensus regarding which patients should receive CNS prophylaxis or which is the most effective delivery method.[2] Overall, the incidence of CNS relapse across all DLBCL subsets is only approximately 5%, but clinical risk factors, including the involvement of specific anatomic sites, are associated with a significantly higher rate of CNS spread. Further, we are beginning to uncover the biological basis for DLBCL involving the CNS, as specific genetic subtypes demonstrate an inherently higher rate of CNS tropism.[3-5] The CNS International Prognostic Index (CNS-IPI) is a commonly used risk model that stratifies patients into risk categories,[6] and combining this model with the cell-of-origin phenotype may improve patient selection.[7] However, even the most robust predictive models cannot overcome the fundamental problem that the chemotherapy agents most effective for the cure of systemic DLBCL do not reliably penetrate the blood-brain barrier (Figure 1).[8] Conversely, methotrexate (MTX), which reliably penetrates the CNS, is not highly effective for DLBCL. The most commonly used prophylactic strategy is repeated intrathecal (IT) injections of chemotherapy such as MTX during front-line therapy, but since brain parenchymal sites are the commonest site of CNS relapse, some advocate the use of deeply penetrant drugs such as high-dose methotrexate (HD-MTX).[9,10] No randomized prospective study has directly addressed this specific question, and, as a result, practice patterns rely on consensus guidelines and vary widely across institutions and individual providers.[11] In essence, the debate about optimal delivery methods is essentially a 'race to the bottom' that compares two strategies that do not adequately address the clinical problem.

Bobillo *et al.* utilize this lack of consensus to retrospectively compare clinical outcomes in 585 patients with DLBCL considered high-risk for CNS relapse (29% of all DLBCL cases screened) treated at their own institution with a variety of CNS prophylactic strategies including no prophylaxis at all.[1] Most (86%) of the 295 patients who received CNS prophylaxis were treated with a median of four IT injections of MTX or cytarabine during front-line therapy while a significant minority (14%) of patients were treated with a median of two cycles of HD-MTX at a median dose of 3.5g/m^2 either during front-line therapy (45% of cases) or immediately following (55% of cases). Notably, 11 (26%) patients who received HD-MTX also received concomitant IT chemotherapy. Importantly, 290 (50%) patients received no form of CNS prophylaxis and these patients were significantly older (median age 72 years). This observation highlights the fact that patient-related factors such as age and perceived ability to tolerate treatment-related toxicity greatly influence treatment decisions beyond prognostic scores and/or involvement of extranodal sites. Since all forms of CNS prophylaxis have clinically meaningful toxicities, this underscores the fact that an important limitation of all available datasets is patient selection bias.

Bobillo *et al.* first confirmed the expected finding that patients with relapse in the CNS had a worse median overall survival of only 4.9 months compared to 17.1 months for those with systemic-only relapse (P=0.03).[1] Regarding efficacy, after a median follow-up of 6.8 years, the 5-year CNS relapse rate was still 5.6% in patients who received any form of CNS prophylaxis, confirming that currently employed chemotherapy strategies are not universally effective. An important observation in this study was that CNS relapses in patients treated with prophylaxis occurred a median of 19 months after front-line therapy compared to only 8 months in patients who received no prophylaxis. As a result, even though CNS prophylaxis appeared to reduce the risk of CNS relapse at 1 year, there was no difference in the 5-year CNS relapse rate between patients who received prophylaxis compared to those who received no CNS prophylaxis (5.6% *vs.* 7.5%) (Risk Ratio 0.76, 95% Confidence Interval: 0.35-1.50). Further, there was no difference in the 5-year CNS relapse risk in patients who received IT MTX compared to those who received HD-MTX, although the number of events was small. Taken together, these data suggest that actual risk reduction of any form of CNS prophylaxis with chemotherapy is likely to be modest at best and currently employed strategies may simply delay the timing of CNS recurrence. These findings also have implications for the reporting of CNS relapse. It is well-described that patients with primary DLBCL of the CNS (PCNSL) often have late relapses, and early reporting of clinical outcomes will miss a significant number of events and may overestimate the true cure rate in subsets of DLBCL with the highest CNS tropism.[12] Many retrospective studies that have described the incidence of CNS relapse do not include long-term follow-up beyond 2 or 3 years and therefore may be underreporting the true incidence.[2]

However, the risk of CNS involvement is not equally distributed across all subsets of DLBCL, which may allow for precision medicine strategies. In fact, DLBCL is not a singular disease but comprises a spectrum of aggressive lymphomas with striking underlying genetic diversity. The current classification system recognizes both ABC DLBCL and GCB DLBCL as distinct molecular subtypes and introduced a new entity, high-grade B-cell lymphoma, defined by the presence of *MYC* and *BCL2*

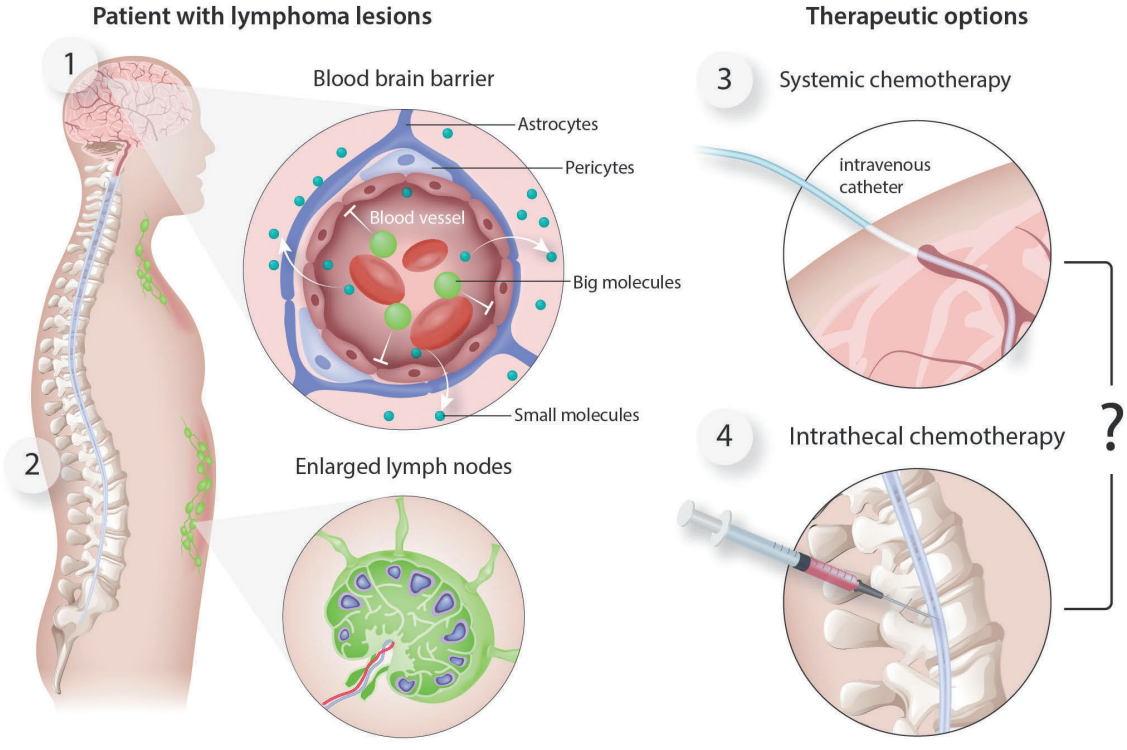

Figure 1. A subset of patients with diffuse large B-cell lymphoma (DLBCL) are at high risk of disease spread to the central nervous system (CNS) and are often treated with chemotherapy prophylaxis. A critical barrier to effective CNS prophylaxis is the blood brain barrier (1) which limits the entry of the chemotherapy agents most effective for systemic DLBCL (2). Current therapeutic options for chemotherapy CNS prophylaxis are systemic chemotherapy (3) or intrathecal chemotherapy (4) which are both limited in efficacy and increase toxicity. Novel small molecule inhibitors are being tested in DLBCL involving the CNS that effectively penetrate the blood brain barrier and may improve treatment options.

and/or *BCL6* rearrangements (HGBCL-DH/TH).[13] Indeed, Bobillo *et al.* observed that patients with ABC (non-GCB) DLBCL subtype had an overall higher risk of CNS relapse in their series.[1] Furthermore, recent multiplatform genomic profiling studies have identified genetic subtypes of DLBCL with shared genetic features.[3,4] One genetic subtype MCD is characterized by frequent co-occurrence of *MYD88*^{L265P} and *CD79B* mutations, prominent immune-editing features, and *PIM1* mutations.[3] These tumors occur almost exclusively within ABC DLBCL and frequently involve extranodal sites including the testes, breast and CNS.[3] It is noteworthy that a separate multiplatform genomic profiling study described a very similar subtype termed Cluster 5 (C5) tumors which were characterized by *MYD88*^{L265P} and *CD79B* mutations, gain of *18q*, and PIM1 mutations, and also exhibited a propensity for extranodal sites, including the CNS and testis.[4] Moreover, a recently reported series of 26 cases of secondary DLBCL of the CNS confirmed a higher prevalence of MCD subtype than observed in a reference cohort of relapsed DLBCL without CNS spread (38% *vs.* 8%; *P*=0.003).[14] In this study, the majority of other DLBCL cases with CNS spread were either HGBCL-DH/TH or associated with *TP53* mutations. Another recent study investigated the genomic predictors of CNS relapse in 82 cases of primary testicular DLBCL, which has a strong predilection for CNS spread.[15] The authors identified *BCL6* and/or *PDL1* or *PDL2* rearrangements as the most common genetic aberrations associated with CNS relapse after treatment for primary testicular DLBCL. Although the precise mechanisms by which various genetic aberrations co-operate to promote CNS spread remains undetermined, these results suggest that a more nuanced understanding of the molecular biology of DLBCL involving the CNS may lead to novel therapeutic targets.

In order to improve clinical outcomes, however, novel therapies with demonstrable efficacy within genetically defined subtypes will be necessary. Multiple clinical studies have reported impressive clinical activity of the Bruton tyrosine kinase (BTK) inhibitor ibrutinib and ibrutinib-based regimens in DLBCL involving the CNS, including patients refractory to chemotherapy.[16,17] Even though a randomized phase III study did not show an overall benefit from adding ibrutinib to R-CHOP as part of front-line therapy for non-GCB DLBCL, certain subsets appeared to have improved outcomes.[18] Further studies of BTK inhibitors with R-CHOP are currently ongoing that should provide additional data regarding rates of CNS relapse. In addition, the immunomodulatory agent lenalidomide has demonstrated good clinical activity and favorable safety in DLBCL involving the CNS.[19] Lenalidomide has also been added to R-CHOP as part of front-line therapy for DLBCL that may benefit certain subsets of DLBCL.[20] The currently available data do not support the use of either ibrutinib or lenalidomide as part of front-line therapy to prevent CNS spread of DLBCL, but all clinical trials testing novel agents should report CNS-specific outcomes within genetically defined subtypes.

In summary, chemotherapy as CNS prophylaxis is not universally effective no matter what the delivery method,

and the prevention and treatment of CNS relapse remains an unmet clinical need in the management of DLBCL. Penetrating the blood-brain barrier is an important consideration, but improved therapies will be required to overcome intrinsic chemotherapy resistance. A nuanced mechanistic understanding of targetable pathways underpinning DLBCL involving the CNS has led to novel targeted agents and immunotherapy approaches that demonstrate promising clinical activity and good CNS penetrance. Novel agents that target oncogenic drivers based on the underlying biology of DLBCL subtypes may ultimately prove to be the most effective way to prevent and/or treat CNS recurrence.

Disclosures

No conflicts of interest to disclose.

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