

Be mindful of the central nervous system in Burkitt lymphoma

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In this issue of *Haematologica*, Zayac *et al.* illustrate the adverse prognostic impact of central nervous system (CNS) involvement for adult patients with Burkitt lymphoma (BL).¹ The authors reported data from a retrospective series of 641 patients treated at 30 institutions in the USA and identified 120 (19%) patients with baseline CNS involvement. In the majority of cases (81%), the leptomeninges were involved, 17% had brain parenchymal lesions, and the site was unspecified in 2%. The risk was not uniformly distributed as patients with concomitant human immunodeficiency virus (HIV) infection had CNS involvement in 30% of cases whereas extranodal disease (particularly testicular involvement), poor performance status, and markedly elevated lactate dehydrogenase level were strongly correlated with CNS spread in HIV-negative patients. Most patients (89%) were treated with one of three standard frontline BL regimens: CODOX-M/IVAC, HyperCVAD/MA, and DA-EPOCH-R, presumably all with curative intent.^{2,4} Notably, active CNS involvement was evenly distributed across the three regimens, although this was not the case for other risk factors. The data clearly demonstrated that baseline CNS involvement

identified patients who are difficult to cure with standard frontline approaches as they had lower rates of complete response (59% vs. 77%; $P < 0.001$) and a significantly lower 3-year overall survival (49% vs. 74%; $P < 0.001$) compared to patients without baseline CNS involvement. Importantly, the negative prognostic impact of baseline CNS involvement was significant for all three regimens.

A second focus of the study was predictors of CNS recurrence in 570 patients treated with the three standard regimens. The overall rate of disease recurrence was 26% and the recurrence involved the CNS in 23% of cases. Most of these recurrences (82%) were isolated to the CNS without concomitant systemic recurrence and 87% occurred within the first year of treatment. These data strongly suggest that current strategies typically fail to eradicate active baseline CNS disease rather than the CNS being a sanctuary site for late relapses. Indeed, patients with baseline CNS involvement had the highest CNS recurrence rate of 18%. Considered by regimen, patients who received DA-EPOCH-R had a 35% rate of CNS recurrence among those with baseline CNS disease. These data illustrate that baseline CNS involvement is a

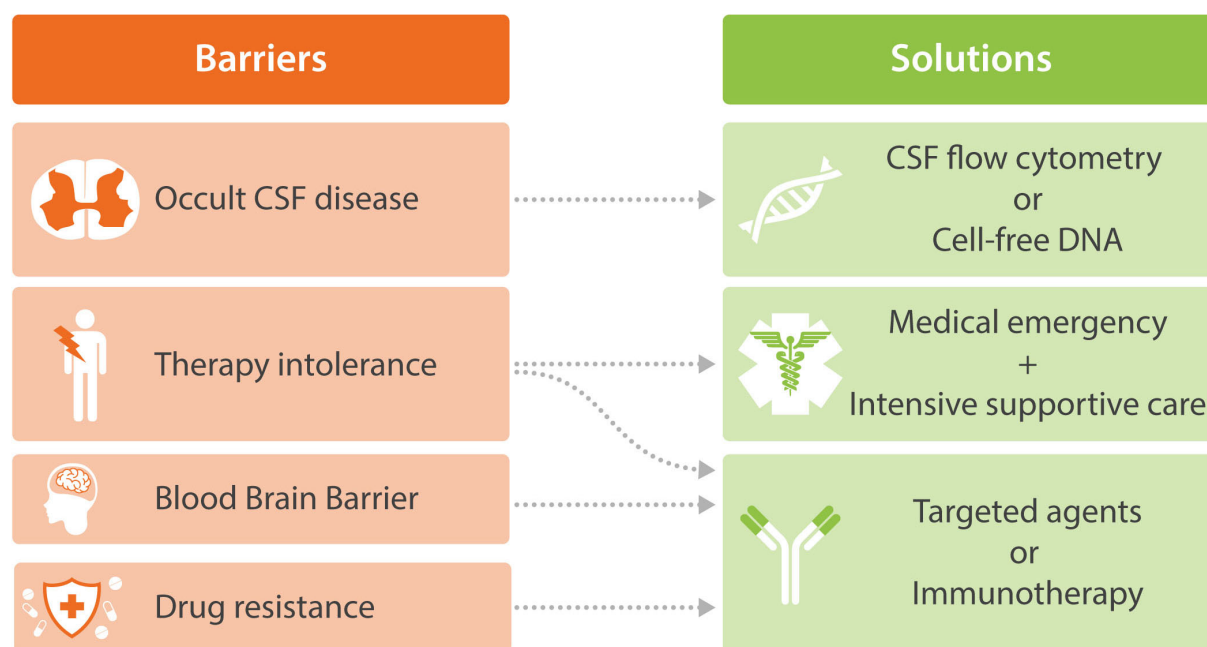


Figure 1. Multiple barriers prevent current strategies from effectively treating and preventing central nervous system disease in adults with Burkitt lymphoma. Routine cytology is insufficiently sensitive for the detection of occult lymphoma cells in the cerebrospinal fluid (CSF) and widespread adoption of more sensitive techniques such as CSF flow cytometry or the development of assays that detect cell-free tumor DNA in the CSF are potential solutions. Therapy intolerance is a barrier unique to adults since pediatric regimens that employ high intensity chemotherapy and are highly effective in children and young adults with central nervous system (CNS) disease are often not tolerated by older patients or those with co-morbid conditions. Treating “possible Burkitt lymphoma (BL)” as a medical emergency with rapid employment of aggressive supportive care can improve performance status to allow for proper CNS-directed interventions and reduce the risk of early toxic death. The blood-brain barrier limits the use of many chemotherapy agents, but novel pathway inhibitors and immunotherapy agents with activity in BL are in clinical development, are often more tolerable, effectively cross the blood-brain barrier, and may overcome chemotherapy resistance. A more complete understanding of the genetic basis for mechanisms of drug resistance in BL may allow the development of additional novel agents that penetrate the CNS.

greater problem in real-world practice than observed in clinical trials, and that isolated CNS recurrence is a common cause of treatment failure in adults with BL. The contributing factors are multiple and one should not conclude that the problem is readily addressed by choice of frontline regimen. In reality, the absence of highly effective CNS-penetrating agents is a major barrier, and new strategies should focus on this limitation (Figure 1). In the meantime, optimal management mandates being ever mindful of CNS detection, prophylaxis, and treatment.

The first important question is whether high-dose methotrexate-containing regimens such as CODOX-M/IVAC or HyperCVAD/MA are superior to DA-EPOCH-R in patients with CNS disease. The inherent selection bias of this retrospective study design precludes a definitive answer since the patients who received DA-EPOCH-R were older and were more likely to have a poor performance status.⁵ It is unclear whether these patients would have even been candidates for highly dose-intensive regimens since toxicities rise sharply with age.^{6,7} In a multicenter study of DA-EPOCH-R in 113 adults with BL, we reported that baseline CNS involvement was associated with an inferior progression-free survival.⁴ Importantly, these patients had equal risk of disease progression as well as early toxic death due to sepsis compared to patients without CNS disease. Intensification of chemotherapy may improve control of CNS disease, but will increase the risk of early toxic death. In reality, only a prospective randomized study, such as the HOVON 127 trial (EudraCT number: 2013-004394-27), can adequately address the question of optimal therapy selection for adults with BL across various subsets.

Careful review of the data in the report from Zayac *et al.* and in the published literature suggests that additional barriers contribute to this complex problem (Figure 1). An important component of proper use of DA-EPOCH-R for BL is a risk-adapted approach that includes a careful analysis of the cerebrospinal fluid (CSF) with flow cytometry to detect occult disease. Using this approach, patients who are positive by flow cytometry are treated with an intensive intrathecal chemotherapy schedule while patients who are negative by flow cytometry receive less intrathecal treatment as CNS prophylaxis. Given the nature of the retrospective study by Zayac *et al.*, the proper use of CSF flow cytometry to identify and adjust treatment with DA-EPOCH-R is unknown as is the use of brain imaging and CSF cytology. The absence of proper CNS evaluation in this series confounds any interpretation that DA-EPOCH-R is less effective than other high-dose regimens. Furthermore, only 45% of the patients received the schedule of intrathecal therapy as published. Lastly, intrathecal chemotherapy alone would not be adequate therapy for brain parenchymal lesions and these patients have been excluded from clinical trials of DA-EPOCH-R; yet four patients in the study discussed had brain parenchymal lesions and received DA-EPOCH-R, which contributed to the high rate of CNS recurrence.

The authors adequately address the limitations of their data and should be commended for performing a sobering analysis of outcomes in adults with BL which we commonly consider “highly curable.” In reality, these data illustrate that we successfully cure fewer adult BL patients than suggested by clinical trials, although the proper implementation of the treatment regimens in general practice likely contributes to this disparity. Advances in the detection of occult CSF disease, including assays for cell-free tumor DNA, may be important in future studies. Perhaps most importantly, these data highlight that no matter which chemotherapy regimen is selected, effective treatment of CNS disease is an unmet need in BL. Novel targeted agents or immunotherapy that can overcome chemotherapy resistance, penetrate the blood-brain barrier, and are tolerated by adult patients of all ages offer the most promise. Sadly, the patients with the highest risk of treatment failure, such as those with CNS involvement or HIV, are often excluded from clinical trials testing these novel agents.⁸⁻¹⁰ Until we collectively change our minds about the wisdom of this practice, we should expect to be disappointed with ‘real-world’ outcomes.

Disclosures

No conflicts of interest to disclose.

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