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https://doi.org/10.1182/blood.2022017645

LYMPHOID NEOPLASIA

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Claiming the mantle of the brain

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In this issue of *Blood*, Rusconi et al provide evidence that ibrutinib improves survival compared with chemotherapy that crosses the blood-brain barrier (BBB) in patients with central nervous system (CNS) relapse of mantle cell lymphoma (MCL).[1]

The development of CNS involvement or CNS relapse poses a significant clinical challenge in the management of MCL. In a retrospective series, the overall incidence of CNS relapse in MCL is uncommon, reportedly in the range of 4% to 5% in unselected cohorts.[2-4] In contrast to diffuse large B-cell lymphoma, the MCL CNS relapse is characterized by more insidious onset, with median time to relapse of 15 to months, more frequent leptomeningeal disease than isolated parenchymal involvement, and a heightened risk in a subset of patients with aggressive disease features such as blastoid histology, high lactate dehydrogenase, high Ki67 (≥30%), and high-risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score, in which the 5-year actuarial risk for CNS relapse could reach 15% to 26%. Historically, the outcome of CNS relapse has been dismal, with median survival at around 5 months after diagnosis of CNS involvement, despite access to systemic treatment with CNS-penetrant drugs such as rituximab and high-dose antimetabolites, although the latter are often prohibitive for patients who are elderly or those with comorbidities. There remains a significant unmet need to develop safe and effective treatment strategies for CNS relapse in MCL.

Improvement in the MCL treatment landscape in the past decade, particularly the introduction of well-tolerated novel targeted therapies in the relapsed or refractory (R/R) setting, has contributed to the overall improvement in treatment responses and survival outcomes in broad-based population studies.[5,6] Several novel agents approved by the US Food and Drug Administration for treating MCL, including ibrutinib and lenalidomide,[7,8] have demonstrated CNS-penetrant activities, which highlight the potential of targeted therapy for CNS disease. In the absence of dedicated prospective data comparing outcome with targeted agents vs high-dose antimetabolite chemoimmunotherapy, careful analysis of real-world experiences after CNS relapse in MCL offers valuable insight on evolving treatment strategy in the era of targeted therapy.

Rusconi and colleagues reported a multicenter retrospective analysis of outcomes in patients with MCL who had CNS relapse and were treated with either ibrutinib or BBB-crossing chemoimmunotherapy between 2000 and 2019. A total of 88 patients with CNS relapse were identified from 38 participating centers within the Fondazione Italiana Linfomi (FIL) and European Mantle Cell Lymphoma Network (EMCLN). Specifically, 29 patients received ibrutinib at the standard dose of 560 mg once per day and 29 received BBB-crossing chemotherapy defined as methotrexate ≥2 g/m^2, cytarabine ≥2 g/m^2, and ifosfamide ≥3 g/m^2, including 18 (62%) who received BBB-crossing treatment in the pre-ibrutinib era. The remaining 30 patients received miscellaneous suboptimal palliation. Unsurprisingly, the ibrutinib cohort had significantly higher median age (67 years vs 60 years; $P = .005$), whereas most other clinical characteristics were comparable for the cohorts treated with either ibrutinib or BBB-crossing therapy. A propensity score based on a multivariable binary regression model was used to minimize selection bias between the ibrutinib and BBB-crossing therapy cohorts because of the nonrandom assignment of clinical variables in retrospective analysis. Ibrutinib treatment was associated with higher response rates (78% vs 46%), superior overall survival (16.8 months vs 4.4 months; $P = .007$), and superior progression-free survival (PFS) (13.1 months vs 3.0 months; $P = .009$), over BBB-crossing therapy. Ibrutinib therapy was the strongest independent predictor for survival in a multivariable Cox regression model. CNS progression of disease >24 months and classical morphology were favorably associated with survival in univariable analysis.

The retrospective study by Rusconi et al represents the largest case series to date and summarizes the best available evidence to support the use of ibrutinib as an effective and safe targeted therapy for ibrutinib-naïve patients with MCL who have CNS relapse. As expected for systemic treatment with ibrutinib, most patients will develop resistance in their CNS. The median PFS for patients receiving ibrutinib for CNS relapse was 13.1 months in their study, which was comparable to the median PFS of 13.9 months reported for systemic R/R MCL.[9] Prospective trials should be encouraged to improve treatment whenever possible, including studies designed for CNS relapses of a variety of B-cell malignancies for which potential benefit in MCL could be extrapolated and further validated.[10] It remains to be determined whether molecular biomarkers such as TP53 are predictive of response or resistance in CNS, and whether high-risk diseases such as those with blastoid morphology would benefit from ibrutinib combinations (eg, with high-dose methotrexate or CNS-penetrant novel agents such as lenalidomide or nivolumab), the next generation Bruton tyrosine kinase (BTK) inhibitors (eg, acalabrutinib and zanubrutinib), or a

non-nonvalent BTK inhibitor (eg, pirtobrutinib) to overcome resistance.

Ultimately, strategies for reducing the incidence of CNS relapse and improving treatment outcome will improve survival. Given the wide adaptation of BTK inhibitors for treating systemic R/R MCL and the clinical activity of ibrutinib in the CNS for patients with MCL, it is worth hypothesizing whether inclusion of ibrutinib in earlier lines of therapy will contribute to CNS protection or at least delay the CNS relapse in high-risk subgroups. Several ongoing randomized prospective phase 3 studies have incorporated BTK inhibitors for induction and maintenance (eg, ibrutinib in SHINE [NCT01776840], ENRICH, and TRIANGLE [NCT02858258]; acalabrutinib in ACE-LY-308 [NCT02972840]; and zanubrutinib in NCT04002297), providing a unique opportunity with data maturation to assess the impact of ibrutinib on the risk and incidence of CNS relapse in randomized controlled data sets with contemporaneous treatment.

The favorable outcome of ibrutinib in the management of CNS relapse of MCL is a welcome option for patients with MCL who frequently are not candidates for intensive chemotherapy regimens. This study extends the therapeutic claim of ibrutinib for MCL to the CNS, as the quest for a cure for this difficult disease continues.

Conflict-of-interest disclosure: J.R. received research funding from Bristol Myers Squibb/Celgene, AstraZeneca, Genentech, and Daiichi Sankyo and served as a consultant for Kite Pharma, Secura Bio, Daiichi Sankyo, and Bristol Myers Squibb/Celgene. ■

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https://doi.org/10.1182/blood.2022017285