blood advances

Ibrutinib in the treatment of relapsed FL and MZL?

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Comment on Nastoupil et al, page 7141

In this issue of *Blood Advances*, Nastoupil et al report the results of a large, phase 3 study (SELENE) investigating whether ibrutinib in combination with standard chemotherapy consisting of bendamustine-rituximab (BR) or rituximab, cyclophosphamide, doxorubicin, and prednisolone (R-CHOP) can significantly improve survival of patients with follicular lymphoma (FL) or marginal zone lymphoma (MZL).[1] Although the study did not meet its end point and the design may not perfectly reflect current practice, prospective randomized studies such as SELENE should remain the cornerstone of practice-changing clinical investigation.

FL represents the most common indolent lymphoma,[2] whereas the various types of MZL account for a smaller proportion of patients with indolent disease.[3] First-line therapy of FL and MZL, nowadays, results in complete and long-standing remissions in the majority of cases. For both FL and MZL, the duration of response, progression-free survival (PFS), and overall survival decrease with increasing lines of therapy; in particular, patients being refractory to first-line therapy or relapsing early after a first remission have a less favorable course. Therefore, improvement of salvage therapy continues to be an unmet medical need.[2,3]

The first-in-class Bruton tyrosine kinase (BTK) inhibitor, ibrutinib, showed efficacy in virtually all B-cell lymphomas, including FL and MZL.[4] The subsequently licensed BTK inhibitors acalabrutinib and zanubrutinib achieved even higher response rates in relapsed and refractory FL and up to 80% in relapsed or refractory MZL.[3] Therefore, combining ibrutinib with the immunochemotherapy backbones R-CHOP or BR based on prior exposure to R-CHOP or BR seemed a logical and promising approach for second- or later-line therapy of FL and MZL.

Nastoupil et al report the results of a prospective, randomized, double-blind, phase 3 study that compared R-CHOP or BR combined with ibrutinib vs the same immunochemotherapy regimens and placebo. More than 400 patients were treated, no major differences in patient characteristics were reported, and >90% of patients received BR with or without ibrutinib. Although the study did not meet its primary end point, the prolongation of PFS (median, 40.5 vs 23.8 months; $P = .092$) by almost 1.5 years is remarkable and certainly demonstrates that BTK inhibitors are active in indolent lymphoma and that adding a BTK inhibitor to BR may be a strategy to consider when other options are not available.

This study was performed in 2014 and 2015 and planned in the years before. Therefore, it does not come as a surprise that this, similar to many other studies conducted in an environment in which new therapies enter the clinical arena faster than any phase 3 study will be completed, can be criticized in various ways. For instance, acalabrutinib, zanubrutinib, or any other investigational BTK inhibitor may show better efficacy and/or less toxicity than ibrutinib. More importantly, in 2023, patients with relapsed or refractory FL or MZL can be treated with a plethora of molecules and modalities that were not readily available at the time this study was planned.

Besides high-dose chemotherapy and autologous stem–cell transplantation, which was administered to a surprisingly low percentage of patients participating in this study, a chemotherapy-free approach combining rituximab with the immunomodulator lenalidomide could be used for second-line therapy. In the AUGMENT trial, lenalidomide has been shown to potentiate the effect of rituximab, more than doubling the PFS as compared with that in the control group receiving placebo.[5]

Other therapeutic options for relapsed or refractory FL are rapidly evolving. After second relapse, patients in many countries, among others, have access to the bispecific antibodies, the enhancer of

zeste homolog 2 inhibitor tazemetostat, phosphatidylinositol 3-kinase inhibitors, or chimeric antigen receptor T-cell therapy.

Although none of these new molecules and modalities will be effective for each individual patient and may cause significant toxicities, they certainly broaden our therapeutic armamentarium. A thoughtful choice of targeted drug(s) for the individual patient, including a perspective on how to sequence treatments in the further course of disease, will undoubtedly prolong the life of many patients affected by relapsed or refractory indolent lymphoma.[6-9] Because multiple therapies are approved, it is not easy to make the most appropriate treatment decision for a given patient. Parameters that affect therapeutic decisions include the age of patient and fitness, individual comorbidities, the number and type of prior lines of treatment, duration of previous responses, tumor burden at relapse, and molecular characteristics of the tumor.[7]

Most importantly, we believe that large well-designed and well-conducted phase 3 studies, as the one reported by Nastoupil et al, should remain the mainstay of clinical research in lymphoma and beyond because only randomized studies with sufficient power to control for random effects will allow for the rational inclusion of new drugs and modalities into the therapeutic algorithm of any disorder without the potential bias inherent to small nonrandomized studies. In that sense, although this study failed to meet its primary end point and potentially better options may be available today to treat relapsed FL and MZL, the investigators of the SELENE study should be congratulated for having conducted this study. With few exceptions, smaller phase 1 or 2 studies selecting for the most promising new agents followed by large phase 3 studies confirming (or not) the improvement assumed with the experimental vs standard therapy remain the only albeit cumbersome way to execute unbiased clinical research.

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References

1. Nastoupil L, Hess G, Pavlovsky MA, et al. Phase 3 SELENE study: ibrutinib plus BR/R-CHOP in previously treated patients with follicular or marginal zone lymphoma. *Blood Adv*. 2023;7(22):7141-7150.
2. Casulo C, Barr PM. How I treat early-relapsing follicular lymphoma. *Blood Adv*. 2019;133(14):1540-1547.
3. Rivero A, Mozas P, Magnano L, López-Guillermo A. Novel targeted drugs for follicular and marginal zone lymphoma: a comprehensive review. *Front Oncol*. 2023;13:1170394.
4. Bartlett NL, Costello BA, LaPlant BR, et al. Single-agent ibrutinib in relapsed or refractory follicular lymphoma: a phase 2 consortium trial. *Blood Advances*. 2018;131(2):182-190.
5. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2019;37(14):1188-1199.
6. Zelenetz AD, Gordon LI, Chang JE, et al. NCCN Guidelines Insights: B-cell Lymphomas, Version 5.2021. Accessed 20 August 2023. https://jnccn.org/view/journals/jnccn/19/11/article-p1218.xml
7. Dreyling M, Ghielmini M, Rule S, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical practicegGuidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(3):298-308.
8. Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. *Lancet Oncol*. 2022;23(8):1055-1065.
9. Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med*. 2022;28(2):325-332.

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