bleomycin, and prednisone (R-ACVBP) for higher-risk patients,[6] the patients in this trial had favorable-risk DLBCL: 56% had sm-IPI of 0, 38% had sm-IPI of 1, and 64% were age <60 years. Therefore, the superb outcomes in this study should not come as a surprise.

The authors state that because 28 of 38 patients in PR achieved CR after additional chemotherapy and/or RT, they think that "PET-positive signals observed after cycle 4 were mainly related to residual lymphoma."[1] An alternative explanation would be that PET was detecting inflammation or effects of neutrophil growth factor use instead of active disease, which then could have resolved on its own. This has been reported particularly with R-CHOP-14, which requires tight PET scanning deadlines, with absolute majority of biopsies of PET$^+$ patients showing no active lymphoma in 1 study.[7] The fact that "the outcome of these PR patients did not differ from those reaching CR after 4 cycles of R-CHOP"[1] could be used to argue that it was not in fact active lymphoma that PET was picking up, because patients who were truly refractory (ie, PR) to 4 cycles of R-CHOP should have had poor outcomes, which was clearly not the case.

Six cycles of R-CHOP as administered in advanced-stage disease remains a viable alternative to the shorter R-CHOP plus RT course, in part based on extrapolation from the MInT (MabThera International Trial) study, which enrolled a significant number of patients with limited-stage disease.[8] Because the impact of RT after a full course of R-CHOP in nonbulky disease remains uncertain, the lack of impact of RT in this study is not surprising, since all patients achieving PR after 4 cycles of R-CHOP and those achieving CR but with sm-IPI of 1 received a total of 6 cycles of R-CHOP. Therefore, the 158 patients in CR with sm-IPI of 0 who were randomly assigned to RT or observation after only 4 cycles of R-CHOP constitute the true experimental arm. In this regard, the trial confirms the British Columbia Cancer Agency experience, where 1 additional cycle of R-CHOP was administered to patients who achieved CR on PET after 3 cycles of R-CHOP, for a total of 4, with OS >90%.[9]

In 2004, Miller[10] published an editorial in which he outlined 3 risk groups based on SWOG S8736. The most favorable cohort (no bulk, sm-IPI of 0) had 5-year OS >90% regardless of treatment strategy, in the pre-rituximab era. A majority of patients in the study by Lamy et al belong to this group. So what is the take-home from this study? The only reasonable conclusion is that if you are such a patient (ie, in CR after 4 cycles of R-CHOP), RT may not be necessary. And thus, we arrive where we started.

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REFERENCES

1. Lamy T, Damaj G, Soubeyran P, et al, on behalf of the LYSA Group. R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. *Blood*. 2018;131(2):174-181.
2. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med*. 1998;339(1):21-26.
3. Persky DO, Unger JM, Spier CM, et al; Southwest Oncology Group. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. *J Clin Oncol*. 2008;26(14):2258-2263.
4. Stephens DM, Li H, LeBlanc ML, et al. Continued risk of relapse independent of treatment modality in limited-stage diffuse large B-cell lymphoma: final and long-term analysis of Southwest Oncology Group study S8736. *J Clin Oncol*. 2016;34(25):2997-3004.
5. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993;329(14):987-994.
6. Récher C, Coiffier B, Haioun C, et al; Groupe d'Etude des Lymphomes de l'Adulte. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. *Lancet*. 2011;378(9806):1858-1867.
7. Moskowitz CH, Schöder H, Teruya-Feldstein J, et al. Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in advanced-stage diffuse large B-cell lymphoma. *J Clin Oncol*. 2010;28(11):1896-1903.
8. Pfreundschuh M, Kuhnt E, Trümper L, et al; MabThera International Trial (MInT) Group. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2011;12(11):1013-1022.
9. Sehn LH. Chemotherapy alone for localized diffuse large B-cell lymphoma. *Cancer J*. 2012;18(5):421-426.
10. Miller TP. The limits of limited stage lymphoma. *J Clin Oncol*. 2004;22(15):2982-2984.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Bartlett et al, page 182

Choosing ibrutinib wisely

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In this issue of *Blood*, Bartlett et al share their experience with the use of ibrutinib in patients with relapsed or refractory follicular lymphoma (FL).[1]

This study was part of a multicenter, international, phase 2 consortium trial that enrolled 40 patients with recurrent FL, who were treated with ibrutinib 560 mg once per day until disease progression. The clinical activity of ibrutinib in this setting was modest, with an overall response rate (ORR) of 37% and a complete response (CR) rate of 12%. The median progression-free survival (PFS) was 14 months, and median duration of response was 13 months. More importantly, this study was able to explore 2 different measures predictive of response to ibrutinib. They included evaluation of the impact of interim positron emission tomography (PET) scan on PFS outcomes, and the correlation of clinical outcomes with recurrent mutations identified in a cancer gene panel that used next-generation sequencing on pretreatment biopsies.

The advent of the irreversible Bruton tyrosine kinase (BTK) inhibitor ibrutinib has been transformational for the management of various B-cell malignancies. Ibrutinib is currently approved for the

treatment of chronic lymphocytic leukemia, Waldenström macroglobulinemia, mantle cell lymphoma, and chronic graft-versus-host disease. However, this report and another report (the DAWN Study [FLR2002]) that included patients with chemotherapy refractory FL show similar activity in this particular patient group.[2] In the final analysis of the DAWN study of 110 patients, the ORR was 20% with a CR rate of 10%. Median PFS was 4.6 months, and time to next treatment was 16 months. These results are consistent in terms of their duration of response and PFS when compared with those reported from other similar studies of novel agents such as idelalisib,[3] copanlisib,[4] umbralisib,[5] and venetoclax,[6] in patients with relapsed or refractory FL, which reflects the challenging clinical scenario.

As seen in other studies of ibrutinib in various B-cell malignancies,[7,8] ibrutinib is generally well tolerated in these heavily pretreated populations, and common adverse effects were cytopenias, infections, diarrhea, hypertension, atrial fibrillation, and bleeding. These adverse events led to discontinuation of ibrutinib in 6% to 10% of patients in both studies of ibrutinib.

In addition to clinical activity, the Bartlett et al study evaluated the role of PET scans as a predictive tool for response to ibrutinib in patients with FL. Although PET scans are not commonly used for managing patients with FL, these were performed in 20 patients after 8 days of treatment with ibrutinib. The maximum standardized uptake value (SUV) assessed on the day 8 scan was found to correlate with both response and PFS. A recursive partitioning algorithm identified a cutoff point of 13.78 for the day 8 SUV that could predict PFS. Although this is an interesting finding, it needs to be further validated in larger trials.

In addition to having a PET scan, 31 patients underwent core needle biopsies of involved lymph nodes before starting ibrutinib, and fresh tissue was snap-frozen and subjected to Illumina HiSeq sequencing. This resulted in identification of multiple genes with various mutations, some of which correlated with outcomes. Importantly, patients with caspase-associated recruitment domain-11 (*CARD11*) gene mutations failed to respond to ibrutinib therapy and also had an inferior PFS. Conversely, patients with other mutations, including those in *IGLL5*, *KMT2D*, and *FOXO1* experienced improved PFS. The presence of a *CARD11* gene mutation as one of the more frequent mutations in FL was initially identified in the GLSG2000 cohort analysis and is part of the m7-FLIPI (which combines the mutational status of 7 genes with the Follicular Lymphoma International Prognostic Index) score developed for FL prognostication and predictive of 5-year failure- free survival.[9] The gene is located on chromosome 7p22.2 and encodes the CARD11 protein, which is a member of the membrane-associated guanylate kinase family and is downstream of SYK and BTK in the B-cell receptor (BCR) signaling pathway. Gain-of-function mutations may result in constitutive activation of NF-κB through its interaction with bcl-10 and independent of the BCR activation.[10] Another important issue to note is that there was a significantly lower response to ibrutinib in patients refractory to rituximab. This correlation with rituximab resistance and *CARD11* mutations is uncertain because 4 of the patients with *CARD11* mutations were refractory to rituximab and 1 was sensitive to rituximab (Nancy Bartlett, written communication, 13 November 2017). Nevertheless, studies like these are essential for identifying subsets of patients a priori in whom certain targeted therapies may not be effective.

What is the place of ibrutinib in the current landscape of FL? Data regarding the use of a CD20 antibody in combination with chemotherapy is very compelling, and this treatment is still considered the standard of care for initial and relapsed treatment of the majority of patients with FL. However for relapsed patients who may not be candidates for a chemotherapy-based regimen, PI3 kinase inhibitors are an acceptable treatment option approved by the US Food and Drug Administration. With existing data on lenalidomide, rituximab, ibrutinib, and venetoclax among others, patients can potentially have access to multiple effective therapeutic options. Nevertheless, every effort should be made to treat these patients on well-designed clinical trials that will hopefully result in addressing the issues of optimal duration, sequencing of treatment, and identification of resistance mechanisms. In addition, it will clarify the need for a maintenance approach.

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REFERENCES

1. Bartlett NL, Costello BA, LaPlant BR, et al. Single-agent ibrutinib in relapsed or refractory follicular lymphoma: a phase 2 consortium trial. *Blood*. 2018;131(2):182-190.
2. Gopal AK, Schuster SJ, Fowler N, et al. Ibrutinib as treatment for chemoimmunotherapy-resistant patients with follicular lymphoma: first results from the open-label, multicenter, phase 2 DAWN study [abstract]. *Blood*. 2016; 128(22). Abstract 1217.
3. Gopal AK, Kahl BS, Flowers CR, et al. Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemo-immunotherapy. *Blood*. 2017;129(22):3037-3039.
4. Dreyling M, Morschhauser F, Bouabdallah K, et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Ann Oncol*. 2017;28(9): 2169-2178.
5. O'Connor OA, Flinn IW, Patel MR, et al. TGR-1202, a novel once daily PI3K-delta inhibitor, demonstrates clinical activity with a favorable safety profile in patients with CLL and B-cell lymphoma [abstract]. *Blood*. 2015;126(23). Abstract 4154.
6. Davids MS, Roberts AW, Seymour JF, et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. *J Clin Oncol*. 2017;35(8):826-833.
7. Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223.
8. Wiczer TE, Levine LB, Brumbaugh J, et al. Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib. *Blood Adv*. 2017;1(20):1739-1748.
9. Pastore A, Jurinovic V, Kridel R, et al. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. *Lancet Oncol*. 2015;16(9):1111-1122.
10. Bertin J, Wang L, Guo Y, et al. CARD11 and CARD14 are novel caspase recruitment domain (CARD)/membrane-associated guanylate kinase (MAGUK) family members that interact with BCL10 and activate NF-kappa B. *J Biol Chem*. 2001;276(15):11877-11882.

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