Check for updates

blood® commentary

CLINICAL TRIALS AND OBSERVATIONS

Comment on Burger et al, page 1011

Targeting CD20 takes the backseat in CLL

John C. Byrd | The Ohio State University

In this issue of *Blood*, Burger and colleagues report results from a randomized phase 2 study combining rituximab and ibrutinib vs ibrutinib alone in high-risk, untreated, and previously treated chronic lymphocytic leukemia (CLL) patients.[1] This well-performed study provides clear guidance to the field of CLL that, unlike chemotherapy, rituximab addition to ibrutinib does not improve progression-free survival (PFS) or overall survival (OS) as compared with ibrutinib alone.

The CD20 antigen that is selectively expressed on mature B cells represents one of the most exploited therapeutic target in the treatment of B-cell lymphoproliferative disorders. The first therapeutic agent to target CD20 was the chimeric monoclonal antibody rituximab. Rituximab has multiple mechanisms of action, including direct killing, antibody-directed cellular cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC). Rituximab demonstrated single-agent activity in a variety of B-cell malignancies, but the benefit was, at most, marginal in CLL. Indeed, it took more than a decade of research to definitively demonstrate a benefit of rituximab, and this only occurred when combined with fludarabine and cyclophosphamide where complete response (CR), PFS, and OS were superior.[2] Efforts to improve on targeting CD20 in CLL occurred by improving CDC, ADCC, and/or direct killing with engineered antibodies such as ofatumumab and obinutuzumab. In the only direct comparison of CD20 antibodies, obinutuzumab was shown to be superior in terms of CR and PFS as compared with rituximab when combined with chlorambucil.[3] At this juncture in CLL clinical care, CD20 antibodies with either rituximab or obinutuzumab in combination with chemotherapy had a definitive role in CLL treatment.

The introduction of targeted therapy with small molecules targeting B-cell receptor signaling (BCR) has dramatically changed the CLL treatment landscape. Most exploited of BCR signaling targets is the Bruton tyrosine kinase (BTK) protein. Ibrutinib was the first irreversible inhibitor to effectively provide continuous inhibition of BTK in tumor cells. Ibrutinib as a monotherapy was shown in multiple studies to be highly active in both symptomatic, previously treated, and also untreated CLL, where response rates exceeded 90%.[4,5] Ibrutinib differs from other treatment previously administered in CLL in not being time limited, continuing until progression or intolerance develops. The durability of PFS on ibrutinib therapy in both untreated and previously treated CLL has been shown to exceed that expected to be observed with other traditional CLL therapies used, including chemotherapy, antibody, and chemoimmunotherapy. A major question facing the field of CLL has been, should CD20 antibody therapy with rituximab be abandoned or added to ibrutinib in building upon the success of ibrutinib? The study presented herein by Burger demonstrates no increased toxicity of the combination of rituximab and ibrutinib as compared with monotherapy with the later agent. Unfortunately, there was an absence in improvement in PFS with relatively long follow-up beyond where expected benefit of the combination would be expected. Indeed, these results were confirmed by a large intergroup study in previously untreated CLL recently, which also demonstrated no benefit to the addition of rituximab to inbrutinib vs the later therapy.[6] However, both of these studies demonstrated the combination had a higher CR and more frequent minimal residual disease negative (MRD^-) at completion of therapy. Do these study findings suggest there is something to build on in a different manner?

Obinutuzumab was shown to be superior to rituximab as a doublet with chlorambucil in previously untreated, elderly CLL patients.[3] One obvious extrapolation would be to suggest a better CD20 antibody, such as obinutuzumab, could be substituted. However, outside of the past experience with chemoimmunotherapy, there is really no rationale for this. Indeed, ibrutinib not only has the potential to antagonize ADCC but also decreases C20 expression on CLL tumor cells during treatment.[7] Identification of an antigen outside of CD20, which is not modulated by ibrutinib or alternatively sequencing treatment not together (as with chemoimmunotherapy) but in parallel, might represent an alternative strategy. In addition, transition to an alternative more selective BTK inhibitor with less influence on natural killer cell ADCC for this combination could be considered. Further confounding the importance of CD20 antibody treatment in CLL is the introduction of the highly active bcl-2 antagonist venetoclax that when combined with either ibrutinib and/or a CD20 monoclonal antibody demonstrates a much higher CR rate than seen with any other CLL therapies.[8-10] However, with the field moving toward an attempt to limit continuous therapy by introducing even the most active combination approaches to yield MRD^- CR after a fixed period of therapy, a small difference in disease reduction might translate to important clinical benefit. It is for this reason that several of the recently initiated phase 3 studies by

Downloaded from http://ashpublications.net/blood/article-pdf/133/10/1003/1556833/blood892695.pdf by guest on 08 June 2024

the US Intergroup (#NCT03737981 and #NCT03701282) will use a triple combination therapy of ibrutinib, venetoclax, and obinutuzumab. In the setting of a clinical trial, it is quite conceivable that a combination of a BTKi together with a CD20 antibody, such as performed by Burger, for a fixed time period of therapy might also achieve a beneficial clinical benefit.

Moving forward, how does the landmark study of Burger and colleagues and the already published North American intergroup study[6] inform the field? In no setting outside of clinical trials should rituximab be administered together with ibrutinib as part of a continuous treatment regimen for CLL. Although the primary end point of the important trial by Burger and colleagues was negative, both this answer and the secondary end points inform the field of CLL research moving forward. Targeting CD20 with therapeutic antibodies as part of future trials should not be abandoned, but adaptation to better molecules, preclinical rationale, and end points with modern therapy should be accounted for.

Conflict-of-interest disclosure: J.C.B. has received research funding from Acerta Pharma, Genentech, Janssen, Verestem, and Pharmacyclics. He is or has been a consultant (<5000 dollars) for Acerta Pharma, Pharmacyclics, Jazz pharmaceuticals, Gilead Pharmaceuticals, and Verastem Pharmaceutics for advice on drug development. ■

REFERENCES

1. Burger JA, Sivina M, Jain N, et al. Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. *Blood*. 2019;133(10):1011-1019.
2. Hallek M, Fischer K, Fingerle-Rowson G, et al; German Chronic Lymphocytic Leukaemia Study Group. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164-1174.
3. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014;370(12):1101-1110.
4. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(1):32-42.
5. O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. *Blood*. 2018; 131(17):1910-1919.
6. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;379(26): 2517-2528.
7. Skarzynski M, Niemann CU, Lee YS, et al. Interactions between ibrutinib and anti-CD20 antibodies: competing effects on the outcome of combination therapy. *Clin Cancer Res*. 2016;22(1):86-95.
8. Rogers KA, Huang Y, Ruppert AS, et al. Phase 1b study of obinutuzumab, ibrutinib, and venetoclax in relapsed and refractory chronic lymphocytic leukemia. *Blood*. 2018; 132(15):1568-1572.
9. Seymour JF, Mobasher M, Kater AP. Venetoclax-rituximab in chronic lymphocytic leukemia. *N Engl J Med*. 2018;378(22): 2143-2144.
10. Wierda WG, Siddiqi T, Flinn I, et al. Phase 2 CAPTIVATE results of ibrutinib (ibr) plus venetoclax (ven) in first-line chronic lymphocytic leukemia (CLL) [abstract]. *J Clin Oncol*. 2018;36(15). Abstract 702.

DOI 10.1182/blood-2019-01-892695

© 2019 by The American Society of Hematology

LYMPHOID NEOPLASIA

Comment on Opstal-van Winden et al, page 1130

Genetic susceptibility to breast cancer in lymphoma survivors

James M. Allan | Newcastle University

In this issue of *Blood*, Opstal-van Winden and colleagues report the results of a genome-wide association study to identify constitutional genetic variants (single nucleotide polymorphisms; SNPs) associated with risk of developing radiation-induced breast cancer in Hodgkin lymphoma survivors.[1] Therapy-induced cancer is a potentially lethal complication of treatment of a first primary cancer, and breast cancer is one of the most common therapy-induced cancers in long-term survivors of Hodgkin lymphoma treated with radiotherapy. Travis et al[2] estimated the cumulative absolute risks of breast cancer following a ≥40 Gy dose at age 25 to be 11% and 29% at 20 and 30 years, respectively. Data from a large cancer registry showed relative risk of breast cancer to be ~6 times higher in Hodgkin lymphoma survivors compared with the general population.[3] As such, the prospective identification of individuals at high risk of radiogenic breast cancer could facilitate improvements in the clinical management of Hodgkin lymphoma patients, reducing subsequent cancer risk and improving outcomes.

Numerous patient- and exposure-related factors modify radiogenic breast cancer risk, including age at exposure, cumulative radiation dose, radiation field size, radiation field location (mediastinal or mantle), and early menopause.[4] Evidence also suggests a role for constitutional genetics as a determinant of individual risk,[5] with the prevailing model suggesting that the genetic contribution to radiogenic breast cancer risk is polygenic and determined by coinheritance of multiple low-penetrance genetic variants in numerous genes.

Based on this premise, Opstal-van Winden and colleagues used an innovative 2-phase approach to identify genetic variants associated with risk of radiogenic breast cancer specifically in Hodgkin lymphoma survivors. Their approach was designed to first identify variants interacting with radiation for breast cancer risk and then use these to generate a polygenic risk score (PRS) for breast cancer in Hodgkin lymphoma survivors while simultaneously eliminating variants associated with Hodgkin lymphoma risk (see figure). Carefully defined inclusion criteria were used to maximize the frequency of likely radiogenic cases while simultaneously minimizing the frequency of "sporadic" second primary breast cancer cases without a radiation etiology. Specifically, the authors restricted their study to cases exposed to radiation at a

Downloaded from http://ashpublications.net/blood/article-pdf/133/10/1003/1556833/blood892695.pdf by guest on 08 June 2024