Managing Lymphoma

BTK inhibitors in CLL and MCL: Strategies for Managing Adverse Events

Julie M. Vose, MD, MBA
Neumann M. and Mildred E. Harris Professor
Chief, Division of Oncology/Hematology
University of Nebraska Medical Center
Omaha, Nebraska

Jeremy R. Stone, MD
Assistant Professor of Cardiovascular Medicine
University of Nebraska Medical Center
Omaha, Nebraska

Nicole Lamanna, MD
Associate Professor of Medicine
Director, Chronic Lymphocytic Leukemia Program
Columbia University Medical Center
New York, New York

Peter Campbell, PharmD, BCOP
Clinical Pharmacy Manager
Hematology/Oncology
Program Director
Post-Graduate Year Two
Oncology Pharmacy Residency
New York-Presbyterian Hospital
New York, New York

What role do Bruton's tyrosine kinase inhibitors (BTKi's) play in the management of chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL)?

Bruton's tyrosine kinase (BTK) is a non-receptor intracellular kinase that belongs to the TEC family of tyrosine kinases. BTK plays an essential role in the initiation, progression, and survival of lymphocytes in B-cell malignancies, and is a critical effector molecule involved in all aspects of B-cell development. Overexpression of BTK in CLL and MCL supports cell survival proliferation; BTK inhibition is therefore an attractive therapeutic target.

There are currently three BTKi's available: first-generation ibrutinib, and second-generation acalabrutinib and zanubrutinib. All three BTKi's have been approved in MCL, and ibrutinib and acalabrutinib are approved for CLL. BTKi's have become one standard of care option for patients with CLL and represent a new option for those with relapsed/refractory MCL. Acalabrutinib has been shown to be non-inferior to ibrutinib, and zanubrutinib has been shown to produce an increased overall response compared to ibrutinib, although how this translates into progression-free survival (PFS) is not yet known.[1,2] However, BTKi's are associated with toxicities that can limit their efficacy. The second-generation BTKi's appear to cause decreased frequency of adverse events (statistically significantly less atrial fibrillation) compared to ibrutinib due to a decrease in off-target effects.[2-4] Still, toxicity causes a significant amount of drug discontinuation. In clinical trials, BTKi discontinuation rates range from 5%-16%, but real-world studies suggest that this rate may be as high as 42%, with more than half (55%) of discontinuations due to adverse events (AEs).[5-7]

Managing BTKi toxicities is challenging. Dose reductions or interruptions in BTKi therapy remains an area of active research, and results are somewhat conflicting. In an analysis of the RESONATE trial, dose interruptions greater than one week reduced PFS among those taking ibrutinib for CLL

or small lymphocytic lymphoma (SLL), but other studies have demonstrated no change in treatment efficacy among those requiring BTKi dose reductions due to concomitant CYP medications or increase post-transplant immunosuppression.[5,8] Every situation is unique, and decisions regarding whether or not to reduce the dose or discontinue a BTKi should be personalized.

What are some of the most common toxicities encountered with BTKi's?

Cardiotoxicity

BTKi's can cause cardiotoxicity via off-target effects on the phosphoinositide 3-kinase (PI3K) pathways. These pathways play a protective role during cardiac stress, and when they are inhibited lead to alterations in the calcium channel, causing action potential prolongation, early and delayed depolarization, and arrhythmias. PI3K inhibition can also cause alpha-adrenergic stimulation, resulting in myocardial dysfunction and/or hypertension.

There are a number of drug interactions between ibrutinib and medications for atrial fibrillation. Diltiazem/verapamil and amiodarone/dronedarone can significantly increase ibrutinib level through CYP450 3A4 inhibition, while the effects of direct thrombin inhibitors such as dabigatran are exacerbated due to P-glycoprotein inhibition caused by ibrutinib. Factor Xa inhibitors and digoxin have similar but more moderate effects stemming from CYP450 3A4 and P-glycoprotein inhibition.[9] Patients with atrial fibrillation who are taking a calcium channel blocker like diltiazem or verapamil who opt to take a BTKi should be switched to beta-blockers whenever possible. Digoxin is also preferred over a calcium channel blocker for rate control, but this agent has a moderate interaction with ibrutinib, so digoxin levels should be monitored carefully in coordination with a cardiologist.

In terms of stroke prevention, traditional risk calculators like the CHA_2DS_2-VAS_C score or the HAS-BLED score do not take into consideration cancer patients and their therapies. Traditional anticoagulants such as factor Xa inhibitors have a moderate level of interaction with BTKi's, and their use should involve close monitoring or switching to an alternate stroke prevention medication. Early trials with ibrutinib showed an increased risk of intracerebral hemorrhage, so anticoagulation should be approached carefully.[10]

Arthralgia/myalgia

BTKi's are associated with arthralgias and myalgias, although the exact mechanisms that cause this are unknown. The incidence varies widely between studies, and the presentation can occur immediately or a year or more after BTKi treatment initiation. Risk factors for this AE include female gender, history of autoimmune disease, and frontline BTKi use.[11]

In terms of management, some patients experience spontaneous symptom resolution without intervention. Patients may try a short trial of non-steroidal anti-inflammatory drugs (NSAIDs) to

see if these agents alleviate symptoms, but prolonged use should be avoided due to bleeding and renal risk. In severe and/or persistent cases, BTKi dose reductions or discontinuation may be considered.

Bleeding risk

BTK plays an important role in platelet aggregation, and inhibition of BTK confers bleeding risk. Ibrutinib is associated with predominantly minor bleeding (ie, grade ≤2 ecchymoses and petechiae) in approximately two-thirds of patients.[12] Major bleeding (ie, grade ≥3, necessitating transfusion or hospitalization) occurs in only 2%-9% of patients.[13] Acalabrutinib monotherapy is associated with less minor (37%) and major (2%) bleeding.[14]

Warfarin should be avoided in patients taking BTKi's. Patients should be educated that commonly encountered bruising seen with BTKi's does not confer an increased risk of major hemorrhage and does not necessitate cessation of therapy. Patients with bleeding should be encouraged to avoid over-the-counter supplements that may exacerbate bleeding risk, such as vitamin E or fish oil. For minor bleeding, temporarily halting BTKi therapy typically resolves bleeding within 2-3 days. For severe bleeds, platelet transfusion is recommended, regardless of platelet count. Patients should communicate with their healthcare professionals about any upcoming surgical procedures so medications can be managed appropriately to reduce bleeding risk.

Infection

BTK and TEC induce a certain amount of inhibition of neutrophils, monocytes, macrophages, and T- and B-lymphocytes. Because BTKi's also inhibit infection-fighting pathways, patients taking these agents are at increased risk for viral, bacterial, and fungal infections. In a landmark analysis, grade ≥3 pneumonia occurred in 12% of those taking ibrutinib.[15] Opportunistic infections, including *Aspergillus fumigatus* and *Pneumocystis jirovecii* (PJP) have also been reported in association with BTKi's.[16,17]

Patients should be counseled on their risk of infection, as well as signs and symptoms that are suggestive of infection. Patients with questionable symptoms should have a complete work-up (in either the in-patient or out-patient setting) with an appropriate index of suspicion for opportunistic infections. In the case of severe infection, BTKi therapy should be paused until a definitive diagnosis is attained and restarted after the patient demonstrates clinical improvement.

Clinicians should ensure that all clinically indicated vaccinations (eg, influenza, pneumococcus) are administered prior to treatment, although live vaccines should be avoided. Although there are some data emerging that patients with hematologic malignancies have inadequate response to the COVID-19 vaccine, at this point, it is still recommended for patients, their family, and close contacts.[18] Patients deemed at high risk for infection (ie, relapsed/refractory or heavily

pretreated patients or those with a prior history of infection) should also be considered for PJP and/or herpes virus prophylaxis on a case-by-case basis.

How can clinicians select the optimal BTKi for each patient?

There are a lot of considerations when selecting BTKi therapy. In terms of pharmacokinetics/pharmacodynamics, zanubrutinib has a longer plasma half-life and once-daily dosing. This could impact medication adherence in patients who value easier, less cumbersome treatment regimens, so clinicians should discuss dosing with their patients to determine whether once- versus twice-daily dosing has a significant impact in their lives.

Tolerability and safety should be considered as well. Although final phase 3 comparison data are pending, second-generation zanubrutinib and acalabrutinib appear to have fewer AEs than ibrutinib, including lower risk for bleeding and atrial fibrillation, and less gastrointestinal and dermatologic toxicity. However, ibrutinib has the longest-term safety data, so clinicians need to keep that in mind.

All BTKi's are substrates of CYP3A4, and drug-drug interactions should always be considered. Patients taking acalabrutinib, specifically, should avoid using all strong CYP34A inhibitors, which include clarithromycin, telithromycin, itraconazole, posaconazole, voriconazole, and protease inhibitors. Ibrutinib and zanubrutinib should be adjusted to 70 mg and 80 mg QD, respectively, in patients taking strong inhibitors. Doses should also be adjusted in those taking moderate inhibitors, which include amiodarone, erythromycin, fluconazole, isavuconazole, amprenavir, fosamprenavir, diltiazem, and verapamil. In these cases, doses should be reduced to 280 mg QD for ibrutinib, 100 mg QD for acalabrutinib, and 80 mg BID for zanubrutinib. In general, zanubrutinib appears to have fewer drug-drug interactions versus ibrutinib and may be preferred in patients who are taking a lot of medications.

As with all cancer therapies, determining whether BTKi therapy is right for any individual patient can be challenging. Clinicians would do well to ensure their knowledge about BTKi mechanisms of action, safety, and efficacy is adequate, and engage in shared decision-making with patients and other medical team members to determine whether BTKi's are appropriate for each patient.

For more information on BTK inhibitors in CLL and MCL, click here.

Provided by MediCom Worldwide, Inc.
This activity is supported by educational grants from Pharmacyclics LLC, an AbbVie Company, and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC and BeiGene, Ltd.

References

1. Ghia P, Pluta A, Wach M, et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *J Clin Oncol*. 2020;38(25):2849-2861.
2. Hillmen P, Eichhorst B, Brown JR, et al. First interim analysis of Alpine study: Results of a phase 3 randomized study of zanubrutinib vs. ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic leukemia. LB1900. Data presented at the European Hematology Association 2021 meeting. https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/330170/peter.hillmen.first.interim.analysis.of.alpine.study.results.of.a.phase.3.html. Accessed September 13, 2021.
3. Kaptein Y, De Bruin G, Emmelot-van Hoek M, van de Kar B. Potency and Selectivity of BTK Inhibitors in Clinical Development for B-Cell Malignancies. *Blood*. 2018;132(Supplement 1):1871.
4. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. *J Clin Oncol*. 2021 July 26 [Epub ahead of print].
5. Barr P, Brown JR, Hillmen P, et al. Impact of ibrutinib dose adherence on therapeutic efficacy in patients with previously treated CLL/SLL. *Blood*. 2017;129(19):2612-2615.
6. Mato A, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: A real-world analysis. *Haematolgica*. 2018;103(5):874-879.
7. Aarup K, Curovic Rotbain E, Enggaard L, et al. Real-world outcomes for 205 patients with chronic lymphocytic leukemia treated with ibrutinib. *Eur J Haem.* 2020;105(5):646-654.
8. Hardy-Abeloos C, Pinotti R, Gabrilove J. Ibrutinib dose modifications in the management of CLL. *J Hematol Oncol*. 2020;13(1):66.
9. Ganatra S, Sharma A, Shah S, et al. Ibrutinib-Associated Atrial Fibrillation. *JACC: Clinical Electrophysiology.* 2018; 4(12):1491-1500.
10. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223.
11. Rhodes J, LoRe VA, Mato AR, et al. Ibrutinib-associated Arthralgias/Myalgias in Patients With Chronic Lymphocytic Leukemia: Incidence and Impact on Clinical Outcomes. *Clin Lymphoma Myeloma Leuk.* 2020;20(7):438-444.e1.
12. Lipsky A, Lozier JN, Wiestner A. Response to Comment on Incidence and Risk Factors of Bleeding-Related Adverse Events in Patients with Chronic Lymphocytic Leukemia Treated with Ibrutinib. *Haematologica.* 2016;101(3):e124-125.
13. O'Brien S, Hillmen P, Coutre S, et al. Safety Analysis of Four Randomized Controlled Studies of Ibrutinib in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma or Mantle Cell Lymphoma. *Clin Lymphoma Myeloma Leuk*. 2018;18(10):648-657.e15.

14. Sharman J, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): A randomised, controlled, phase 3 trial. *Lancet.* 2020;395(10232):1278-1291.
15. Coutre SE, Byrd JC, Hillmen P, et al. Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies. *Blood Adv*. 2019;3(12):1799-1807.
16. Rogers K, Mousa L, Zhao Q, et al. Incidence of opportunistic infections during ibrutinib treatment for B-cell malignancies. *Leukemia.* 2019;33(10):2527-2530.
17. Ryan C, Cheng MP, Issa NC, et al. Pneumocystis jirovecii pneumonia and institutional prophylaxis practices in CLL patients treated with BTK inhibitors. *Blood Adv.* 2020;4(7):1458-1463.
18. Blood Cancers Diminish Response to COVID-19 Vaccine. *Cancer Discov*. 2021;11(7):OF4.