Managing Lymphoma

Arthralgias/Myalgias Associated with Targeted Therapy for CLL/SLL/MCL

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How do targeted therapies work to interfere with the pathophysiology of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), and mantle cell lymphoma (MCL)?

The primary targeted therapies that are used to treat CLL, SLL, and MCL are Bruton's tyrosine kinase inhibitors (BTKi's). These drugs work by blocking the B-cell receptor signaling pathway, which is critical for signaling to leukemia and lymphoma cells to promote growth, differentiation, and survival. BTK is a member of the TEC kinase family that plays a significant role in B-cell development. When B-cell receptors are stimulated, BTK is activated, which results in increased level of intracellular calcium and activation of transcription factors that are involved in B-cell proliferation, differentiation, and survival. These effects are not limited to just healthy B cells; this kinase plays a key role in migration and survival of malignant B cells as well. BTKi's, therefore, are believed to bind and obstruct pro-survival signals produced by impaired adhesion properties within cancerous cells. Essentially, BTK is involved in keeping the malignancy healthy and growing; these drugs block BTK, which keeps the pathway from functioning.

What are the side effects associated with these agents?

One downside to BTKi's is the fact that they can cause multiple adverse effects (AEs). Landmark clinical trials of ibrutinib, a first-generation BTKi, determined that AEs lead to clinically significant rates of treatment discontinuation or dose reduction. In the phase 3 RESONATE trial, AEs contributed to a 14% rate of dosage reduction, while 10%, 5%, and 6% of subjects discontinued treatment due to AEs in years 1, 2, and 3, respectively.[1] Real-world studies indicate an even more significant impact of AEs on treatment cessation; 42% of patients discontinue ibrutinib during early treatment, and half of those who discontinue do so because of AEs.[2] This underscores the need for careful management of treatment-emergent toxicities to ensure treatment continuation.

Some of the most common side effects encountered with BTKi's include bleeding and bruising, diarrhea, nausea, heartburn, and skin rash.[1,3-5] Depending on the specific BTKi used, risk for

atrial fibrillation is approximately 3%-10%.[1,3-5] Over time, patients taking BTKi's often develop high blood pressure, which requires monitoring and medical intervention in some cases. Connective tissue side effects are common with BTKi's. Patients may demonstrate skin and nail changes, with brittle, ridged nails that crack easily. These connective tissue effects also produce arthralgias and myalgias, which are some of the most bothersome side effects that patients report. Patients often describe arthralgias that are migratory in nature and can sometimes be debilitating.[6] Clinical trials of ibrutinib have reported arthralgias and myalgias in 11%-36% of patients.[5] While the majority of these arthralgias/myalgias are considered mild or moderate (grade 1-2), these AEs are among the top reasons for discontinuation of ibrutinib.[6] In a real-world retrospective analysis of ibrutinib-treated patients who discontinued therapy, arthralgia was the most common toxicity, leading to treatment discontinuation in nearly half of previously untreated patients.[6] In this study, the median time to ibrutinib discontinuation for arthralgia was 5 months.[6] Factors that increase the risk for arthralgias/myalgias include female gender, younger age (<65 years), history of autoimmune disease, and frontline BTKi use.[5]

The causative mechanism of arthralgia/myalgia associated with BTKi treatment is not yet understood but is believed to be an off-target product of these drugs. Ibrutinib inhibits the activity of at least three major off-targets: epidermal growth factor (producing skin toxicities); interleukin-2 inducible kinase (which impairs the cytotoxic actions of natural killer cells); and the TEC family of kinases (inhibiting their ability to aid in phosphorylation).[7-10] Second-generation BTKi's such as acalabrutinib and zanubrutinib have improved safety profiles, with generally lower rates of discontinuation due to side effects compared with ibrutinib.[11,12] These advantages extend to arthralgias and myalgias. In a recent randomized phase 3 trial comparing acalabrutinib with ibrutinib in previously treated CLL, 15.8% of those being treated with acalabrutinib reported any grade arthralgia, while 22.8% of those treated with ibrutinib reported this AE.[11] Likewise, in the phase 3 ALPINE trial comparing zanubrutinib to ibrutinib in relapsed or refractory CLL, the reported rate of arthralgia in the zanubrutinib treatment arm was 9.3%, compared with 14.0% in the ibrutinib treatment arm.[12] It is likely that the lower incidence of arthralgia and other side effects associated with these second-generation agents is due to less impact on off-target kinases, as these agents are more specific BTKi's compared with first-generation ibrutinib. Of note, the incidence of side effects associated with second-generation inhibitors appear to plateau within the first year of treatment. This differs from ibrutinib, which appears to induce cumulative damage to some systems, such as the vascular system, over time.

How do you manage arthralgias and myalgias in BTKi-treated patients?

Most cases of arthralgia/myalgia will develop within the first several months of treatment initiation and if these side effects are mild, observation is typically recommended. However, when symptoms begin to affect activities of daily living, dosage reductions may be advisable. More severe arthralgia/myalgia (grade 3 or 4) should be managed with treatment

discontinuation, although rechallenge at lower doses is a reasonable approach if symptoms resolve. There has been no formal study of pharmacotherapy to mitigate arthralgia, but pain relievers such as acetaminophen can be effective for reducing low-grade arthralgia. NSAIDs should be avoided if possible secondary to increased bleeding risk. More severe arthralgia may be managed with a short course of steroid therapy such as prednisone as well.

It is also important that patients receive upfront counseling about the risk for side effects associated with BTKi's. If patients understand that they are likely to experience arthralgias, but that these symptoms may get better over time, this information can help them persist with the therapy for the first couple of months, leading to better overall medication compliance. Because these agents are intended to be taken long term, or even indefinitely, treatment adherence within the first several months is crucial, and providing this kind of information can make the difference between treatment success and discontinuation.

What investigational treatments and/or approaches may reduce the side effects associated with BTK inhibition?

One promising theme that is being explored with the combination of BTKi's with other effective drugs, such as venetoclax, as a method of achieving a deep response and thereby limiting the duration of therapy and the potential for long-term side effects. Primary analysis of the phase 3 GLOW study determined that ibrutinib and venetoclax was superior to obinutuzumab and chlorambucil in CLL, with the implication that the deeper, more durable response produced from this combination may enable treatment-free periods.[13]

Additionally, there are now third-generation BTKi's that are anticipated to have even less off-target effects. For example, pirtobrutinib is an investigational non-covalent BTKi that was recently found in the phase 1/2 BRUIN study to be not only effective, with an overall response rate of 63%, but also well-tolerated, with very few grade 3 events and no dose-limiting toxicities.[14] In this trial, the most common adverse events of any grade were fatigue (20%), diarrhea (17%), and contusion (13%); arthralgia was reported in just 11% of the treatment population.

What final thoughts do you have on BTKi's and associated arthralgia/myalgia?

BTKi's are a highly effective class of agents for CLL, SLL, and MCL. However, the toxicities of these agents can limit their effectiveness if not handled properly. While some AEs, such as atrial fibrillation and bleeding, may pose more risk to the patient, clinicians should not underestimate the impact of more 'nuisance' AEs such as arthralgia/myalgia, which is responsible for the majority of treatment discontinuations. BTKi's are only able to be effective if they are dosed optimally and used continuously, so arthralgia/myalgia can significantly impact the efficacy of these treatments. It is therefore critical that clinicians engage in patient education and ongoing

monitoring to ensure that these AEs do not negatively impact patient quality of life and overall outcomes.

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

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