Managing Lymphoma

Cardiology-related adverse events of targeted therapies for CLL/SLL and MCL

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What are targeted therapies for chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL), and mantle cell lymphoma (MCL) and how do these agents cause cardiotoxicity?

The primary class of targeted therapies for these leukemias/lymphomas are Bruton's tyrosine kinase inhibitors (BTKi's). BTKi's really have become the standard first-line therapy in CLL in select patients and represent an exciting new option for relapsed or refractory MCL. Bruton's tyrosine kinase (BTK) is an intracellular kinase that belongs to the TEC family of tyrosine kinases that plays an essential role in the initiation, progression, and survival of lymphocytes in B-cell malignancies.[1] BTK plays a central role in the signal transduction of the B-cell antigen receptor (BCR), which triggers a signaling cascade that supports B-cell survival, proliferation, and differentiation.[1] In CLL and MCL, there is overexpression of BTK, which perpetuates cell survival and production. This makes BTK an attractive therapeutic target.

Unfortunately, BTKi's tend to have off-target effects, which can lead to toxicities. Cardiotoxicity is mostly thought to be mediated through the interference of BTKi's with phosphatidylinositol 3-kinases (PI3K) isoforms. Although the PI3K pathway is normally cardioprotective, as it is activated under times of cardiac stress, the off-target inhibition of PI3K by BTKi's leads to alteration of calcium channel currents in cardiomyocytes which may result in arrhythmias like atrial fibrillation.[1] Additionally, the alpha-adrenergic stimulation caused by BTKi's may lead to myocardial dysfunction and hypertension.

What are the cardiovascular adverse events (AEs) that have been observed in clinical trials and real-world studies?

The most prominent cardiovascular AEs that have been reported in both clinical trials and in the real world have mainly been hypertension and atrial fibrillation (AF). In a pooled analysis of more than 1,500 CLL and MCL patients enrolled in four large randomized clinical trials (RCTs) of ibrutinib – a first-generation BTKi – the incidence of AF was 6.5%, while rates of hypertension associated with ibrutinib were approximately 4%-5%.[2-4] However, these rates may be greater in actual real-world practice. A recent real-world evaluation of ibrutinib in 562 patients with B-cell

malignancies showed that 78.3% of these individuals developed new or worsening hypertension over a median of 30 months.[5] Likewise, real-world follow-up of the Swedish 'compassionate use' cohort identified an AF rate of 8% at 10 months of ibrutinib therapy and 15% at 30 months, implying that the risk of AF is substantial during long courses of treatment.[6]

The toxicity profile of ibrutinib has been the impetus for the development of more selective second-generation BTKi's such as acalabrutinib and zanubrutinib. RCTs of CLL patients have shown that acalabrutinib therapy is associated with an AF rate of 4%-5% and a hypertension rate of 3%-5%.[4,7,8] Notably, a head-to-head trial of acalabrutinib and ibrutinib showed a lower incidence of AF and any-grade hypertension in acalabrutinib-treated patients versus ibrutinib-treated patients.[9] Still, like ibrutinib, real-world studies suggest that the rate of AF associated with acalabrutinib may be higher than that observed in RTCs.[10] Regarding zanubrutinib, RCTs of CLL/SLL patients demonstrate an AF rate of about 3%[11]; again, when compared to ibrutinib, the AF rate associated with zanubrutinib is significantly lower.[12]

What steps can be taken to prevent cardiovascular AEs in patients taking BTKi's?

There are certain risk factors that increase the likelihood for developing AF in those taking BTKi's, including older age (>65 years), hypertension, hyperlipidemia, and a personal history of AF. Additionally, evidence of left atrial enlargement by echocardiography also has been associated with increased risk for AF in patients receiving ibrutinib. Interestingly, previous use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-renin blockers (ARBs), beta blockers, and aspirin is also linked to increased risk for AF in patients receiving ibrutinib. Therefore, oncologists should carefully consider these factors when selecting patients for BTKi therapy and perform a thorough risk-benefit analysis before prescribing these agents in at-risk patients. Additionally, presence of these risk factors should guide oncologists to select second-generation BTKi's wherever possible, as these agents are associated with lower rates of cardiotoxicity.

How can these cardiotoxicities be managed once they occur?

Management of adverse cardiovascular events in patients receiving BTKi's is challenging due to the drug-drug interactions discussed earlier. However, there are some key points that can help to guide practice. When AF occurs, it is best to avoid non-dihydropyridine calcium channel blockers and digoxin for rate control, and instead opt for beta blockers, which are considered safe in this situation. This is because non-dihydropyridine calcium channel blockers inhibit CYP 450, which can lead to a significant increase in ibrutinib levels in these patients. If a rhythm control strategy is necessary, amiodarone and dronedarone should be avoided due to significant interactions with BTKi's, and any other choices for antiarrhythmic therapy should be made with the help of a heart rhythm specialist.

AF always confers a significant thromboembolic risk. For stroke prevention, a careful risk-benefit discussion regarding the initiation of anticoagulation should be held with the patient, the oncologist, and the cardiologist. Typically, the CHA2DS2-VASc and HAS-BLED scores can be used to determine if patients would benefit from anticoagulation and if they have an acceptable bleed risk. Unfortunately, these scores do not incorporate malignancy or the inherent bleeding risk of BTKi's, so the decision should be individualized on a case-by-case basis. If it is determined that patients would benefit from anticoagulation, factor Xa inhibitors such as apixaban and rivaroxaban are considered safest, although they still confer a residual bleed risk due to a mild drug-drug interaction with BTKi's. Caution is therefore recommended in this setting. Other anticoagulants like warfarin should be avoided in this patient population due to an increased risk for intracerebral hemorrhage.

If hypertension occurs, clinicians should follow the 2020 International Society of Hypertension practice guidelines, which recommend first-line pharmacotherapy with ACE inhibitors/ARBs or dihydropyridine calcium channel blockers like amlodipine or nifedipine (but not non-dihydropyridine calcium channel blockers, which are not safe in these patients).[13] If a patient's blood pressure is resistant to treatment, cardio-oncologist involvement is highly recommended.

What is the role of the cardiologist or the cardio-oncologist in the management of CLL/SLL and MCL patients taking BTKi's?

Multidisciplinary involvement is essential when managing these complex CLL/SLL and MCL patients. Oncologists are challenged to be aware of potential AEs of BTKi's that can affect any number of organ systems, so cardiologists or cardio-oncologists can help by paying particular attention to the potential cardiotoxicities that may occur. Moreover, discontinuation of BTKi's is accompanied with its own set of cardiovascular considerations, such as the natural normalization of blood pressure, and cardiologists are often more experienced with down-titration of hypertension medications than the average oncologist. These cardiovascular specialists are also more likely to be familiar with current guidelines, and more likely to interpret these guidelines within the context of malignancy.

In conclusion, BTKi's hold great promise for CLL/SLL and MCL, and as with any cancer therapy, the goal is for the patient to continue therapy for the entire recommended duration. Cardiologists/cardio-oncologists can help to prevent and manage the cardiovascular toxicities associated with BTKi's so patients can gain the maximum benefit from these life-saving drugs.

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