Anticoagulant Use in Patients with Ibrutinib-Related Atrial Fibrillation

**TO THE EDITOR:** We read with great interest the article by Al-Jammali and colleagues (June 2019 issue), which discussed the challenges associated with the use of anticoagulants for patients who have atrial fibrillation after starting treatment with ibrutinib. We believe that this topic is very timely, given the widespread use of ibrutinib in clinical practice; however, we would like to raise some concerns.

As the authors pointed out in their article, most of the clinical studies of ibrutinib report relatively low rates of atrial fibrillation, in the range of 3% to 8%. Nonetheless, the study by Woyach and colleagues (which was not cited by Al-Jammali and colleagues) noted atrial fibrillation rates of 17% with ibrutinib monotherapy and 14% with ibrutinib in combination with rituximab.

These conflicting findings suggest some degree of uncertainty about the magnitude of this complication, particularly among elderly patients with chronic lymphocytic leukemia who are more prone to atrial fibrillation. The study by Mato and colleagues provides real-world evidence showing a 25% incidence rate of atrial fibrillation secondary to front-line ibrutinib treatment. It is also important to emphasize that a temporal relationship exists between the duration of ibrutinib treatment and the onset of atrial fibrillation, which potentially increases up to approximately 16% after at least 2 years of therapy. This may provide a plausible explanation to the observed discrepancies in the rates of atrial fibrillation reported across these various studies.

The recommendations for anticoagulant selection by Al-Jammali and colleagues are in line with those by Ganatra and colleagues. Of note, another underlying challenge that was overlooked is the choice of agent used for rhythm or rate control, given that some of those medications interact with ibrutinib, thereby creating an additional layer of complexity that clinicians have to consider.

Al-Jammali and colleagues stated that atrial fibrillation is a class effect of Bruton's tyrosine kinase (BTK) inhibitors and could also be observed with acalabrutinib. It is worth noting that acalabrutinib is a highly selective BTK that was developed to mitigate some of the off-target effects observed with ibrutinib. Because atrial fibrillation was not detected in any of the clinical studies of acalabrutinib, this drug may be reserved as an alternative to ibrutinib treatment in patients with atrial fibrillation. Yet, a study by Awan and colleagues lists 4 (approximately 10%) cases of arrhythmia after patients switched from ibrutinib to acalabrutinib as a result of intolerance to ibrutinib (2 cases were in the setting of pulmonary infections, the third case was secondary to previous treatment with ibrutinib, and the fourth was de novo supraventricular tachycardia). Given the small number of patients included in this study, larger studies are needed to determine whether acalabrutinib is a safer option than ibrutinib, particularly among patients at risk for atrial fibrillation.

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**AUTHORS’ RESPONSE:** We would like to express our appreciation for the comments and issues raised by Dr Hamadeh and Dr Arnall regarding our recent review of anticoagulation challenges with ibrutinib-induced atrial fibrillation. We share the same concerns as our col-

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leagues regarding the increased long-term use of ibrutinib and the emerging associated side effects with the therapeutic challenge to mitigate such adverse events.

Regarding the reported incidence of ibrutinib-related atrial fibrillation, the 6% to 9% incidence rate is consistent with pivotal clinical trials of ibrutinib use. We agree with Hamadeh and Arnall in that with increased use, the incidence of ibrutinib-related atrial fibrillation is expected to rise as more patients have their disease being controlled with ibrutinib therapy for a longer duration. The study by Woyach and colleagues presents higher incidence rates of atrial fibrillation than those reported in previous phase 3 clinical trials. In that study, the incidence of grade 3 atrial fibrillation was 8%, which is 2 to 3 times higher than the 2% to 3% incidence rate reported in pivotal landmark trials.

Although this discrepancy between the studies is concerning, it is unclear whether an age difference is the reason for such a discrepancy, because the median age in the studies by Woyach and colleagues and Burger and colleagues was approximately 73 years (range, 65-89 years) with an approximately 65% male patient population. Although both studies had similar age and sex distributions, the same cannot be said for other risk factors for atrial fibrillation. The underlying cardiac pathology at baseline was not fully disclosed in the published studies, which can be a major contributor to the discrepancy in the incidence of atrial fibrillation.

Choosing the appropriate strategy (rate vs rhythm control) for the management of atrial fibrillation remains a challenge. As with patients without cancer, the patient’s age, duration of atrial fibrillation, patient preference for therapy, and underlying cardiac pathology should be taken into consideration before choosing one control strategy over another. We believe that the same approach should be used when deciding which strategy to pursue and what class of medication is the safest.

Of the available medications for rate and rhythm control, nondihydropyridine calcium channel blockers are the most likely to interact adversely with ibrutinib. Beta blockers, dofetilide, sotalol, flecaïnide, and amiodarone are not known to have severe pharmacokinetic interactions with ibrutinib. Given the lack of evidence regarding which treatment strategy should be considered for ibrutinib-induced atrial fibrillation, we did not feel strongly about the need to address the role of different antiarrhythmic medications in our review.

We respectfully agree with Hamadeh and Arnall that switching between ibrutinib and acalabrutinib therapies can be considered an option for ibrutinib-induced atrial fibrillation, given the lower reported incidence of atrial fibrillation with acalabrutinib. One challenging issue with this approach, aside from the paucity of evidence, is that acalabrutinib is not yet investigated for all indications for which ibrutinib is currently indicated, such as nonlymphoma and nonleukemia indications (eg, chronic graft-versus-host disease).

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