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EDITORIAL COMMENT

Cardiotoxic Atrial Fibrillation With Novel Cancer Treatment

More Relevant Than We Think*

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Bruton's tyrosine kinase inhibitors (BTKi) are novel oral cancer therapies that have revolutionized the treatment of chronic lymphocytic leukemia (CLL) and other malignancies.[1-4] However, BTKi is associated with an increase in atrial fibrillation (AF) and other arrhythmias.[5-8] To date, the bulk data evaluating cardiotoxic risk with BTKi have primarily focused on CLL-predominant populations. Yet, increasing data have established the efficacy of ibrutinib and other BTKi in various lymphoma populations.[9,10] Historically, the incidence of AF and other cardiac events have been less well-recognized in lymphoma trials primarily focused on anticancer efficacy. As such, there is limited availability of systematic arrhythmia data, particularly beyond CLL. Because of this and the limited available robust cardiac data definitely describing the risk of AF and its implications among BTKi-treated populations beyond CLL, further investigation is needed.

In this issue of *JACC: Advances*, Ojo et al[11] identified patients initiating BTKi therapies and other anticancer treatments in the setting of a non-Hodgkin lymphoma diagnosis. The cohort included a total of 1,957 patients from a retrospective database divided into 3 arms: patients on BTKi treatment (n = 197; mainly ibrutinib), non-BTKi treatment (n = 859), and no treatment (n = 901). BTKi therapy included 90% ibrutinib and 10% acalabrutinib. Where available, observed AF reporting rates were compared to age, sex, and cardiovascular risk factor-adjusted rates. Within this, AF rates reached 25% by 5 years post-BTKi therapy initiation and were >500% higher than traditional risk-predicted rates. Treatments outside of BTKi are associated with a 1.8-fold increase in AF. Risk factors associated with AF development include older age, male sex, hypertension, and any lymphoma treatment. The development of incident (new) AF after any lymphoma treatment is associated with an up to ~4-fold increase in subsequent mortality. Notably, the authors report several interesting findings. First, BTKi use (mainly ibrutinib) is associated with a >5-fold increase in AF among lymphoma patients, with an incidence rate of 25% by 5-years. Second, any lymphoma treatment is linked with some increase in AF. Third, the development of any AF after cancer treatment initiation is associated with an up to nearly 4-fold increase in long-term mortality (HR: 3.98, 95% CI: 2.51-6.33). Fourth, 53% of patients with AF received anticoagulation. Finally, they observed a nearly 3-fold increase in mortality following new AF development after BTKi-therapy initiation (HR: 2.83, 95% CI: 1.25-6.38).

These findings add to a growing body of evidence demonstrating significant AF elevation with BTKi therapies. It also further establishes that AF may be even more common with ibrutinib and other BTKi therapies than initially recognized. In the only prospective systematic longer-term electrocardiographic monitoring study of BTKi-treated patients, a surprising 38% of CLL patients developed AF by 2-year follow-up.[6] In an evaluation of landmark phase II

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and III cancer trials, AF and other cardiac events appear to have been significantly underreported by well over 2-fold.[12] Similarly, in a separate systematic review of monotherapy trials, ibrutinib was associated with a nearly 5-fold increase in the annual rate of AF development.[13] Further, in an evaluation of nearly 300 ibrutinib-treated CLL patients, AF development led to a >3-fold increase in long-term mortality.[14] Notably, the current investigation adds to our understanding of the impacts and relevance of cardiotoxic AF after a cancer diagnosis.

Although observed AF rates were elevated, the true incidence of cardiotoxic AF with BTKi, particularly beyond ibrutinib, is largely unknown. This current study by Oja et al[11] raises attention to the importance of close monitoring for cardiotoxicities such as AF after initiation of certain cancer therapies. This study was able to show that BTKi therapy, mostly ibrutinib, increases the risk for AF more than other lymphoma treatment options such as anthracycline, monoclonal antibodies, and immunotherapy. It is well established in previous studies that ibrutinib increases the risk of AF, which is the most common cause of therapy discontinuation.[15] In the current study, Ojo et al,[11] for the first time, demonstrate the magnitude of increase in AF among primarily lymphoma patients treated with BTKi therapies. They also identify key risk factors, including age >64 years, male sex, and hypertension. These observations may prove vital, given the limited available data describing the true incidence and impact of AF after anticancer therapy initiation. Yet, as most AF is paroxysmal and up to 70% of even noncancer events are asymptomatic,[16] the true burden of AF is likely greater than current estimations. The incidence of AF in this study is also likely underestimated due to lack of guidelines for continuous cardiac monitoring after anticancer therapy initiation and enrollment of only symptomatic patients.

The exact mechanism(s) behind BTKi-induced AF are not fully understood. In mice models, it was found that long-term exposure to ibrutinib leads to AF development through cellular remodeling, marked by early injury with immune cell response, histologic fibrosis, and cardiac chamber dilation.[17] Similarly, available myocardial biopsy data in patients with ibrutinib-induced cardiotoxicity have also documented the presence of myocardial fibrosis following ibrutinib treatment.[18] These observations are supported by cardiac magnetic resonance data, demonstrating a profound increase in fibrosis among patients with suspected ibrutinib-induced cardiotoxic arrhythmias.[19] These support exaggerated cardiovascular remodeling as a phenotype induced by BTKi therapy.[17,19,20] Yet, beyond alteration or interruption of cancer treatment therapies, the exact pathways to increased mortality remain unexplored.

Putting these data into context raises a number of key questions. 1) What is true rate of incidence of AF with BTKi, particularly next generation BTKi like acalabrutinib and zanubrutinib? 2) What is the optimal strategy for routine screening for AF and other arrhythmias (eg, ventricular arrhythmias) following BTKi therapy initiation? 3) Is it cost-effective to screen all BTKi-treated patients for AF with "long-term" ambulatory rhythm monitors? 4) Would targeted mechanistic strategies reduce cardiotoxic AF risk? The current study provides insights into what we may be missing with BTKi while spurring consideration for further studies of the drivers and optimal management strategies of cardiotoxic AF.

Despite remaining questions, this study provides impetus for further studies to investigate the true burden and impact of AF among cancer patients receiving BTKi and other cancer therapies. It also adds impetus for systematic investigation of the incidence, mechanisms, and potential preventative strategies for cardiotoxic AF after cancer treatment initiation.

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