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EDITORIAL COMMENT

Atrial Fibrillation With Modern Cancer Treatment

More Common Than We Think*

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Atrial fibrillation (AF) is an increasingly common limitation of effective cancer therapy.[1,2] Historically, AF has often been under-recognized given the focus on anticancer drug efficacy in many clinical trials.[3] Most anticancer drug trials do not report AF or other arrhythmias until symptoms are severe enough to require immediate medical attention or they are detected on office electrocardiography. Yet emerging data suggest that AF may significantly affect cancer treatment and survival outcomes in many populations.[4,5] This is often the result of necessary alterations in cancer treatment, the need for anticoagulation strategies in patients with frequent thrombocytopenia who are prone to serious bleeding, and the increased risk for stroke, heart failure, and other major cardiovascular events induced by AF development in patients with cancer. Because of this, and the limited available data definitively describing the risk for these AF events with most cancer treatments, further investigation is needed.

In this issue of *JACC: CardioOncology*, Alexandre et al[6] identify reporting patterns and rates of AF in cancer monotherapy clinical trials. The systematic review included 191 phase II and III clinical trials registered on ClinicalTrials.gov testing 19 anticancer drugs as monotherapy for varying malignancies, among 26,604 patients. Where available, observed AF reporting rates were compared with matched placebo arm rates. Within this, in those trials reporting any AF outcomes, the investigators identified a summary annualized incidence rate of 0.26 to 4.92 per 100 person-years for AF reporting associated with anticancer drug exposure. Notably, the investigators report several interesting findings. First, no systematic or specific AF detection strategy was reported and/or implemented in any of these trials, outside of the use of 12-lead electrocardiography in cases of AF-related symptoms. Second, no trial detected or evaluated for asymptomatic AF. Third, several drug trials did not report the presence or absence of AF. Fourth, higher annualized incidence rates of AF were observed in hematologic malignancy drug trials. Hematologic malignancies were over-represented compared with solid malignancies in trials reporting AF. Finally, the investigators observed an increase in annualized incidence rates of reported AF with 5 drugs, including higher rates of 4.92 (95% CI: 2.91-8.31) with ibrutinib, 2.38 (95% CI: 0.66-8.55) with clofarabine, and 2.35 (95% CI: 1.78-3.12) with ponatinib per 100 person-years for AF reporting, respectively. The risk was highest among younger ibrutinib-treated patients, a population with presumably lower traditional cardiovascular risk. This was compared with an annualized incidence rate of 0.25 per 100 person-years (95% CI: 0.10-0.65) for AF reporting in the placebo arms.

These findings add to a growing body of evidence demonstrating that AF development with several anticancer therapies may be more common than previously thought. In an evaluation of landmark latter phase (II and III) anticancer trials, AF and other cardiovascular events appear to have been significantly under-reported.[3] In a World Health

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Organization spontaneous reporting pharmacovigilance analysis of the VigiBase database, an increase in AF reports was observed among 19 therapies.[7] Similar signals were noted in a retrospective U.S. Food and Drug Administration reporting-based analysis, wherein many common anticancer therapies, including ibrutinib, clofarabine, and ponatinib, were associated with an increase in AF reports.[8] This trend was also noted in a similar VigiBase analysis focusing on anticancer therapies and the development of ventricular arrhythmias, in which 49 therapies were associated with an increased likelihood of potentially fatal arrhythmias' being reported.[9] As many of these events are noted after clinical approval, there is increased urgency to identify these events in novel anticancer therapies prior to their large-scale use. For example, despite the ongoing development of alternative Bruton's tyrosine kinase inhibitors, review of the available data suggests that the residual risk for AF likely remains elevated (eg, a one-third reduction from >500% AF risk with ibrutinib still translates to a nearly 300% elevation compared with expected).[10] Yet the impact of these and other cardiotoxic events on long-term outcomes is largely unavailable.

Although selected AF rates were elevated, the true incidence and impact of AF with most cancer therapies are largely unknown. This is due to the inconsistent nature of AF capture and the absence of rigorous or continuous rhythm monitoring during and shortly after cancer treatment. AF events may often be insidious, as even in patients without cancer, 87% of those with AF do not report any symptoms, an effect that may be amplified in a population focused primarily on cancer control.[11] Yet in several cancer populations, the development of any AF leads to increased longer term mortality.[4,5] With most cancer treatments, AF develops within the first year of treatment, providing an opportunity for the implementation of targeted monitoring strategies. Given the rapidly rising number of patients surviving after an initial cancer diagnosis, but treated with drugs with significant or largely unknown cardiotoxic risk, the effects on outcomes of cardiotoxic AF development may remain to be determined.

The mechanisms for AF with most anticancer therapies are incompletely understood. In preclinical models, long-term ibrutinib treatment induces cellular remodeling, marked by early injury with immune cell response, histologic fibrosis, and cardiac chamber dilation.[12] Available myocardial biopsy and cardiovascular magnetic resonance imaging data from patients with suspected cardiotoxicity have also documented the presence of myocardial fibrosis following ibrutinib treatments.[13] With other drugs, including ponatinib, similar myocardial remodeling effects were observed in histologic evaluation of those with cardiotoxicity development.[14] Despite variations in implicated signaling pathways, these studies consistently support exaggerated adverse cardiovascular remodeling as a key step in increased AF susceptibility with cancer treatments. These alterations are recognized to drive disproportionate manifestations of cardiovascular disease in other populations.[15] However, with proarrhythmic cancer drugs, prospective and mechanistic studies are needed to elucidate the targetable pathways and effects of cardiotoxic events.

Putting these data into context raises a number of key questions. 1) What are the true incidence and burden of AF and other serious arrhythmias (eg, ventricular arrhythmias) with novel anticancer therapies, when extended or continuous electrocardiographic monitoring is used? 2) How does "silent" AF affect survival outcomes among patients with cancer? 3) What are the best strategies to detect AF in novel anticancer therapeutic trials? 4) What are the targetable mechanisms of AF with anticancer therapies? and 5) Would targeted cardioprotective therapies reduce AF risk? The present study provides an important glimpse into what we might be missing in patients with cancer receiving novel therapies, while prompting the need for further evaluation and closer monitoring for AF in novel anticancer trials.

Despite remaining questions, this study provides provocative data for future investigations focused on defining the effect of these and other emerging cancer drugs on incident AF risk. It also adds compelling impetus for more rigorous investigation of the incidence, burden, predictive factors, and impacts of incident AF development after cancer treatment initiation.

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