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EDITORIAL COMMENT

Atrial Fibrillation in Patients With Cancer

A Persistent and Increasing Challenge*

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Atrial fibrillation (AF) is a highly prevalent disease and is particularly common among patients with cancer.[1] The incidence of AF varies on the basis of the population studied and the screening method implemented but conservatively affects more than 30 million patients worldwide.[2-4] Although the annualized incidence of AF in patients with cancer is higher than in the general population, there is also known variability in the incidence depending on the patient, cancer type, and anticancer drug studied.[1,5,6] Notably, studies have also demonstrated a bidirectional link between AF and cancer whereby there is a higher incidence of AF in patients with cancer, and patients with AF have an increased incidence of cancer.[7-9] Recent research has investigated the association between AF and cancer in relation to specific anticancer treatments such as traditional cytotoxic chemotherapies, radiation therapy, targeted therapies, and immunotherapies.[6] Despite increased recognition, data on the true incidence and pathophysiology of AF due to anticancer drugs with known proarrhythmic effects are still limited.[1,5]

In this issue of *JACC: CardioOncology*, the study by Alexandre et al[10] helps address this issue and provides insights into the incidence of AF associated with exposure to 15 anticancer drugs used as monotherapy in phase II and III clinical trials across several cancer types. Using publicly available data from the ClinicalTrials.gov database, the investigators conducted a comprehensive random-effects safety meta-analysis of 191 oncological clinical studies among 26,604 patients to determine the annualized AF incidence rate related to exposure to specific anticancer drugs. The study revealed that the incidence of AF associated with the anticancer drugs studied ranged from 0.26 to 4.92 per 100 person-years, compared with a lower annualized incidence of 0.25 per 100 person-years in placebo-treated patients. The investigators found 485 cases with new-onset AF, and the incidence of AF risk with ibrutinib, clofarabine, and ponatinib was 4.92, 2.38, and 2.35 per 100 person-years, respectively. In addition, subgroup analyses showed higher annualized incidence rates with anticancer drugs used in hematologic malignancies, particularly in acute leukemias.

The investigators should be commended for their thoughtfully conducted study, which advances our knowledge of the proarrhythmic risk of oncotherapeutic agents. The study has significant strengths, including a large sample size, the use of a publicly available database for clinical trials with requirements for standardized reporting, and the inclusion of commonly used cancer drugs. Furthermore, these results are broadly consistent with those of prior population-based studies and add to the growing body of evidence of AF reporting in patients with cancer.[6,8,11,12]

A significant focus of this study was the analysis of clinical studies of anticancer drugs used only as monotherapy. Because of this, 2,069 of the initial studies (81%) in which patients were treated with combination regimens were excluded, potentially resulting in a selection bias and reduced applicability of the results. As the investigators note, this approach precluded estimation of the annualized incidence rates of AF due to drugs known to be associated with AF, such as anthracyclines, cisplatin, and obinutuzumab. The investigators used the Pharmacoepidemiological

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Research on Outcomes of Therapeutics by a European Consortium checklist, a tool designed to assess the risk for bias in observational pharmacovigilance studies. This methodological approach helped account for the potential variability among analyzed studies. However, using this single tool may not be suitable for evaluating the risk for bias in all research studies, particularly randomized controlled trials, which constituted 47% of the clinical studies analyzed.

It is worth noting certain limitations, such as the retrospective design of the study and the reliance on reported adverse events as part of clinical trials to ascertain diagnoses of AF. It is known that the threshold for reporting AF as a severe adverse event in clinical trials may vary, leading to inconsistencies when comparing results across different studies. Specifically, severe cases requiring medical attention may be identified, while asymptomatic cases may be under-reported. Because of the underdiagnosis of AF in the literature and oncological clinical trials, the investigators acknowledge that the true incidence of AF in this study may have also been underestimated compared with the real-life AF incidence in patients with cancer. It is also notable that the calculated AF risk was unadjusted by AF risk factors because of a lack of access to baseline data on patient comorbidities in the study, and this could have influenced some of the results, as adults with combinations of known risk factors are at increased risk for incident AF.[13]

Despite these limitations, many of which are inherent in the design, this study is the first large-scale analysis documenting annualized AF incidence linked to specific drugs compared with placebo-treated patients. The investigators highlight the systemic underidentification of AF among cancer trial patients and raise the critical issue of the heightened risk for thromboembolism and fatal complications due to undiagnosed AF in this population.

Given the rapidly increasing number of oncotherapeutic agents under development and their potential combinations in hundreds of clinical trials, accurate identification of signals for proarrhythmia due to specific drugs has become increasingly challenging. Data from studies such as that of Alexandre et al[10] demonstrate the need for better approaches to the safety assessment of novel oncotherapeutic agents through collaborative efforts among researchers, industry, global regulators, and clinicians. In the future, implementing a standardized approach to cardiac monitoring in oncology trials will be essential to determining the true incidence of AF. Leveraging mobile and wearable technology for longitudinal monitoring may be a promising strategy that warrants further investigation.

This is an exciting time for the cardiovascular care of oncological patients. AF is a significant issue in cardio-oncology, and there is a rapid evolution in our understanding of the pathophysiological basis of AF in patients with cancer and how the mechanisms of action of emerging therapies influence the natural history of AF. This study provides important new information on heightened AF risk due to specific anticancer drugs. It also highlights the opportunity for future basic and translational research to study the role of biology and genetics in the personalized management of arrhythmogenesis in the context of these therapies.

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