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EDITORIAL COMMENT

Unmasking the Hidden Risk

Atrial Fibrillation in Patients With Breast Cancer Treated With Aromatase Inhibitors*

Hidehira Fukaya, MD, PhD

There has been growing attention on the field of cardio-oncology. Advances in chemotherapy for cancer have improved overall survival; however, the cardiotoxicity associated with those treatments has become a significant concern. Significant progress has been made in understanding the cardiovascular effects of cancer and its treatment, and there is a growing need to manage the cardiovascular side effects of therapy, optimizing the overall health and quality of life of cancer survivors.

While cardiotoxic effects, such as heart function impairment due to anthracycline-based chemotherapies and QT prolongation caused by various anticancer drugs, are well known, the diversity of chemotherapy regimens has led to reports of various cardiac side effects.

Breast cancer is one of the most common malignancies, and with the advancement of treatment, the 5-year survival rate has significantly increased.[1] Some cases of breast cancer show hormone-dependent proliferation and hormone therapy can effectively prevent cancer progression. Selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) act differently in estrogen modulation and have unique cardiovascular implications. AIs act as an antagonist for aromatase, the key enzyme to transform androgen to estrogen in peripheral tissues other than ovaries, whereas SERMs directly inhibit estrogen receptors. Although SERMs are antagonistic to the estrogen receptor, they are also agonistic to the cardiovascular system.[2,3]

Focusing on the arrhythmia, polymorphic ventricular tachycardia (torsades de pointes) associated with QT prolongation and atrial fibrillation (AF) are prevalent under chemotherapy. It has been reported that estrogen and androgen affect the ventricular repolarization. AIs potentially reduce circulatory estrogen, resulting in the QTc interval shortening,[4] while SERMs interestingly prolong the QTc interval. Therefore, AIs were reported not possibly to increase the torsades de pointes due to QT prolongation. On the other hand, because a decrease in estrogen has been previously reported to be associated with the new onset AF,[5] those 2 drugs could differently affect the incidence of AF.

In this issue of *JACC: Asia*, Ho et al[6] conducted a retrospective study to investigate the incidence of arrhythmia in breast cancer patients treated with tamoxifen, one of the SERMs, and AIs. The study included 5,942 patients treated with aromatase inhibitors (n = 5,104) or tamoxifen (n = 838) from 1999 to 2020 in Taiwan. In a 21,301 patient-year follow-up, the group treated with AIs had a significantly higher incidence of arrhythmia (crude HR: 2.30; 95% CI: 1.17-4.52; $P = 0.02$). Further analyses showed that the increased arrhythmia risk was driven by the occurrence of new onset AF (crude HR: 2.30; 95% CI: 1.17-4.92; $P = 0.02$), whereas the incidence of ventricular arrhythmias did not differ ($P = 0.83$). After adjustment using Cox proportional hazards regression analysis, AI was an independent risk factor for new onset AF (adjusted HR: 2.06; 95% CI: 1.00-4.24; $P = 0.02$). Furthermore, propensity score matching was also performed as the sensitivity analysis and revealed that AIs showed a significant increase in the incidence of AF. Regarding the incidence of other cardiovascular events, AIs had a higher incidence of ischemic stroke (crude HR: 3.07; 95% CI: 1.51-6.24; $P = 0.002$) and myocardial infarction (crude HR: 2.91;

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From the Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Japan.

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95% CI: 1.07-8.00; $P = 0.04$). However, after adjustment by Cox proportional hazards regression, those became insignificant. Therefore, they concluded that AIs were associated with an increased risk of AF.

Although hormone therapy had been thought to increase the risk of cardiovascular events, including arrhythmias, potent evidence on the risk of AF had been scarce. Therefore, this paper unmasked the hidden risk of AF under the treatment of AIs compared with SERMs. However, this study has several limitations. Aromatase inhibitors are used in postmenopausal cases, while tamoxifen is used in premenopausal cases, meaning the patient populations for the 2 drugs are inherently different. Therefore, while multivariate analysis and propensity score matching were performed, it remains unclear whether the pre- and postmenopausal status themselves did not have an influence. Nevertheless, observing that AF incidence differed between these 2 therapies was crucial and gave us clinically significant information.

As the field of cardio-oncology continues to grow, a deeper understanding of the cardiovascular implications of hormonal therapies is essential for cardiologists. Future prospective studies, including diverse patient populations, would be necessary to validate these findings. Integrating cardio-oncology into routine oncological care could pave the way for holistic patient management, marrying the dual goals of effective cancer treatment and cardiovascular health.

In conclusion, the interlink between oncology and cardiology is becoming increasingly evident. As we strive for better cancer treatments, it is imperative that we remain vigilant to the cardiovascular implications, ensuring that our quest for a cure does not inadvertently compromise heart health.

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ADDRESS FOR CORRESPONDENCE: Dr Hidehira Fukaya, Department of Cardiovascular Medicine, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan. E-mail: hidehira@med.kitasato-u.ac.jp.

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