JACC: CARDIOONCOLOGY VOL. 5, NO. 5, 2023

EDITORIAL COMMENT

Endothelin-1

Is it Time to "Biomark" the Cardiac-Tumor-Treatment Nexus in Breast Cancer?*

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The endothelium-derived 21-residue vasoconstrictor peptide, endothelin (ET), was first isolated and cloned almost 40 years ago and characterized as "one of the most potent vasoconstrictors known."[1,2] Since then, 3 ET isoforms (ET-1, ET-2, and ET-3), 2 canonical G-protein-coupled receptors (ET_A and ET_B), and 2 ET-converting enzymes (ECE-1 and ECE-2) were identified, and their main functions have been widely investigated, including their roles in heart failure, atherosclerosis, chronic kidney disease, hypertension, and pulmonary hypertension.[2] The major isoform of ET expressed in the cardiovascular system is ET-1,[3] which is produced in cardiac myocytes and the vascular endothelial cells and contributes to the regulation of cardiac function vascular tone and peripheral resistance in heart failure.[4] However, although ET-1 concentrations are increased in patients with heart failure with reduced ejection fraction (HFrEF)[5,6] and preclinical studies suggested a cardiac pathological role for elevated ET-1,[7-10] clinical trials of ET-1 receptor blockade in HFrEF patients demonstrated no benefit and even evidence of harm.[11,12] We showed that ET-1 levels were also increased in patients with heart failure with preserved ejection fraction (HFpEF) and that treatment with a dual ET_A/ET_B antagonist abrogated cardiac hypertrophy and adverse cardiac remodeling in an experimental HFpEF model.[10]

It has also been suggested that ET-1 acts as a key signaling messenger in numerous human cancers, with aberrant activation of the ligand, ET-1, and its receptors all contributing to cancer initiation, growth, and progression in a variety of cancer types.[13] In this issue of *JACC: CardioOncology*, Maayah et al[14] report the role of ET-1 as a potential mediator of cardiac remodeling in breast cancer and suggest that ET-1 receptor blockade plays a role in cardiac health in patients with breast cancer.

Observational studies have identified an elevated risk of atherosclerotic cardiovascular disease (ASCVD) mortality in females with breast cancer.[15] Several mechanisms have been proposed, including the "multiple hit" hypothesis suggesting that the combination of underlying risk factors for ASCVD (eg, age and tobacco use), early or delayed cardiotoxicity caused by anticancer therapy, lifestyle perturbations during and after treatment (sedentary lifestyle), metabolic alterations (obesity), and decline in cardiovascular reserve results in a higher risk of ASCVD. Additionally, ASCVD and breast cancer share common biological pathways that may explain disease progression, such as systemic inflammation and oxidant stress, which allow for the activation of cellular processes that underlie both diseases.[16] However, there is limited understanding as to the role that malignant cells per se may have in the development of cardiovascular disease (CVD).

Given that ET-1 has a pathogenic function in CVD, the potential of breast cancer cells to synthesize and express ET-1,[17] and the prognosis value of ET-1 for breast cancer recurrence,[18] we read the article by Maayah et al[14] with the utmost interest.

These investigators performed a retrospective study of 28 women with breast cancer to investigate the contribution of the ET system to breast cancer-induced cardiac remodeling. The quality of these

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2023.05.007

JACC: CARDIOONCOLOGY, VOL. 5, NO. 5, 2023
OCTOBER 2023:701–703

analyses was limited given the lack of patient information in the current study such as prior/other cancers, concurrent/prior medications (eg, statins, other cardiovascular medications, hormone use, and so on), and coexistent comorbidities (other than diabetes or hypertension because these were excluded; eg, tobacco use, atrial fibrillation, hyperlipidemia, and so on). The new data in the current report were also constrained to cardiac magnetic resonance of the right ventricle because the authors acknowledge that the left ventricular (LV) data were previously presented.[19] In addition to the very small sample size of 28 patients, 86% (n = 24) had a recent lumpectomy within a median of 44 days before cardiac magnetic resonance. Thus, the notion of an ET-1-secreting breast cancer tumor inducing cardiac changes during the blood draw and cardiac magnetic resonance measurements is limited. Although the authors' hypothesis is compelling, additional and much larger studies are needed to assess meaningful associations between cardiac structure and function in breast cancer and explore if this is indeed caused by activation of the ET-1 axis.

The preclinical portion of the study is not exempt from limitations. Changes in cardiac function were minimal. Importantly, although the authors state their mouse model of breast cancer shows signs of cardiac remodeling, this was only seen in LV dimensions because there was no evidence of cardiac hypertrophy or fibrosis. Both control and breast cancer mice had similar relative heart weight and LV mass, and there was no difference in transcript expression in cardiac collagen 1a1, 1a2a, or 3a1. Similarly, interstitial fibrosis, as assessed by picrosirius red staining, was not different between groups. Moreover, there was no evidence of cardiac inflammation or oxidative stress in this breast cancer mouse model. These limitations make it unclear as to whether treatment with an ET_A blocker mitigates adverse cardiac remodeling in breast cancer. Perhaps the use of an alternative breast cancer *in vivo* model should have been explored to determine if there was indeed a cardiac phenotype before in-depth mechanistic studies.

Cardiac risk factors and existing CVD at the time of the initial cancer presentation impact the choice of oncology treatments and outcomes in breast cancer patients. Similarly, during breast cancer treatment, prevention and management of cardiotoxicity are essential to minimize the potentially deleterious impact of the therapy on cardiovascular health.[20] Thus, it is critical that the mechanisms underlying the cardiac-tumor-treatment nexus are investigated so as to develop new therapies for the treatment of cardiac disease in breast cancer. The multifaceted role of the ET-1 axis and its role in breast cancer and CVD has been subjected to study in recent years.[21] Although the actions of ET-1 can be complex,[22] there is growing evidence that targeting its signaling may represent a promising therapeutic strategy in various conditions to improve patient outcomes. As such, further studies are needed to decipher the mechanisms underlying ET-1-mediated effects in cancers and develop novel targets to intervene and mitigate the adverse effects of breast cancer on cardiovascular health and vice versa.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Sam is a full-time employee of Eli Lilly and Co and holds a joint, academic appointment at Boston University School of Medicine. This publication is solely from The Sam Lab, Whitaker Cardiovascular Institute at Boston University School of Medicine and has not been funded nor supported by Eli Lilly and Co. This editorial reflects the views of the authors and should not be construed to represent the views or policies of the U.S. Food and Drug Administration nor Eli Lilly and Co. Dr Valero-Muñoz has reported that she has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS **breast cancer, cardiac remodeling, endothelin-1, therapeutic strategies**