JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 1, 2022

EDITORIAL COMMENT

The Quest for an Early Marker of Anthracycline-Induced Cardiotoxicity*

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Significant advances in therapy have greatly reduced cancer-related mortality. Nonmalignant comorbid conditions have become important determinants of quality of life and overall survival. Among this heterogeneous group of comorbid conditions, cardiovascular diseases are major contributors to overall morbidity and mortality in cancer survivors.

Anthracyclines are a class of anticancer drugs that are used to treat many cancers and that have been registered by the WHO in the list of essential medicines. However, anthracyclines display a cardiotoxicity effect that can ultimately culminate in heart failure (HF). Given the growing rate of cancer survivorship, the clinical significance of anthracycline-induced cardiotoxicity (AIC) is an emerging medical issue. Contemporaneous data show that >35% of patients receiving anthracyclines develop any form of cardiotoxicity.[1] AIC can lead to HF, which is associated with massive personal and societal burden. Not surprisingly, interest in preventing, minimizing, or delaying these cardiotoxic side effects remains high and continues to foster research.

Although we have been aware of AIC for many years, there are important unmet clinical needs, such as the lack of accurate markers for its early detection, and the lack of preventive therapies.

Although AIC is a complex entity affecting several cardiac functions, such as contraction, relaxation, coronary physiology, and microcirculation among others, its diagnosis is mainly based on the deterioration left ventricular (LV) systolic function. Current clinical practice guidelines define AIC as a numeric deterioration in left ventricular ejection fraction (LVEF). However, once LVEF is deteriorated, there is already significant cardiac damage, and the chances for restoring normal function are low. Therefore, there is a need to identify markers that are apparent before irreversible damage has occurred.

Echocardiography-based global longitudinal strain has become the current standard because it identifies AIC before overt LVEF deterioration has occurred. Despite occurring earlier than LVEF deterioration, global longitudinal strain abnormalities also occur at a time when macroscopic damage has taken place. Parametric cardiac magnetic resonance (CMR) imaging has been shown to identify one of the earliest phenomena associated with AIC, intracardiomyocyte edema. T2 relaxation time prolongation has been shown to occur before any deterioration in LV systolic function, both in large animal models and in pilot clinical studies.[2,3] CMR has the limitation of the time of scan, which is longer than 45 minutes. This is a limitation for vulnerable patients, such as those with cancer. To overcome this limitation, a revolutionary CMR methodology that allows a massive reduction in scan time (from 45 minutes to <1 minute) has recently been developed.[4] This methodology is currently being tested in oncology patients and is not widely available yet.

Another important venue of research relates to the use of circulating biomarkers as early indicators of AIC. Some studies have identified N-terminal pro-B-type natriuretic peptide, troponin, high-sensitivity C-reactive protein, myeloperoxidase, and growth differentiation factor-15 as potential markers that can

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* 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 2452-302X https://doi.org/10.1016/j.jacbts.2021.11.010

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 1, 2022
JANUARY 2022:11–13

increase the prediction of cardiac dysfunction associated with cancer therapies. Despite intense research, to date none of these markers is accepted as a robust and specific early marker of AIC.

In this issue of *JACC: Basic to Translational Science*, Thompson et al[5] present paraoxonase-1 (PON-1) as a new biomarker associated with AIC. PON-1 is a high-density lipoprotein–associated enzyme that prevents oxidized low-density lipoprotein formation. PON-1 enzymatic activity has been associated with atherothrombotic events and with poor outcomes in patients with HF, but it has never been tested in the cardio-oncology field. In the present study, PON-1 enzymatic activity was serially quantified in a cohort of >200 breast cancer patients who received doxorubicin ± trastuzumab. Serum PON-1 activity was measured at baseline, halfway (1 month), and at the end of doxorubicin therapy (2 months). Echocardiograms were performed at baseline, 5 months, and then yearly. Overall, PON-1 activity decreased over time with doxorubicin. Conversely, increased in the PON enzymatic activity of PON-1 from baseline to doxorubicin completion (not halfway treatment) was associated with AIC.

The study is performed by a respected group in an important prospective cohort study. However, there are some limitations to the study, such as the lack of high-density lipoprotein concentration determination, which could have influenced the associations observed. In addition, not all patients underwent imaging at all timepoints. The fact that changes in PON-1 enzymatic activity from baseline to halfway doxorubicin therapy (1 month) were not associated with the development of AIC casts doubts about its potential as an early biomarker that could have impact on global management of patients.

The mechanism behind the association between increased PON-1 activity and AIC is unknown, but it might reflect an activation of a defense mechanism against exaggerated (lipid?) oxidation entailed by doxorubicin. If this was the case, this biomarker could be further exploited in monitoring responses to potential antioxidant cardioprotective therapies, such as statins. This could be potentially important because there is a need to identify therapies that can prevent AIC, and early trials usually rely on surrogate endpoints. Several interventions have been tested in the past, although none of them has shown robust benefits in terms of AIC prevention. These trials have tested the effect of classical anti-HF therapies (beta blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers) at the time of initiation of chemotherapy without resulting in a reduction in AIC. The specific pathophysiology of cardiac dysfunction in AIC makes it difficult to translate these drugs, which have been shown to be beneficial in other forms of HF (ie, coronary heart disease, dilated cardiomyopathy, etc), to this new setting. One promising intervention currently being tested is remote ischemic conditioning, which has been recently shown to prevent AIC in a translatable large animal model.[6] Currently, remote ischemic conditioning is being tested in lymphoma patients undergoing doxorubicin therapy at high risk for AIC within an ongoing European Commission-funded study (RESILIENCE [Remote Ischemic Conditioning in Lymphoma Patients Receiving Anthracyclines]). Interestingly, remote ischemic conditioning has been shown in another study to be associated with a reduction in antioxidative stress mediators.[7] We speculate that PON-1 activity might also identify subjects responding to remote ischemic conditioning during the course of anthracycline therapy.

In summary, the study by Thompson *et al*[5] opens new venues for the use of novel biomarkers in the management of patients undergoing cancer therapy. Future studies should confirm the value of serum PON-1 activity as a biomarker identifying patients vulnerable to AIC, and eventually to monitor response to therapies that work through a reduction in anthracycline-induced cardiac oxidative stress.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Ibanez is supported by the European Commission (H2020-HEALTH grant Nº 945118 and ERC-CoG grant Nº 819775) and by the Spanish Ministry of Science and Innovation (MCN; 'RETOS 2019' grant Nº PID2019-107332RB-I00). The CNIC is supported by the ISCIII, the Ministerio de Ciencia e Innovación, and the Pro CNIC Foundation, and is a Center of Excellence Severo Ochoa. Dr Moreno-Arciniegas has reported that she has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS cardiac dysfunction, cardiotoxicity, doxorubicin, heart failure, paraoxonase-1