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EDITORIAL COMMENT

Preventing the Cancer Patient of Today From Becoming the Heart Failure Patient of Tomorrow*

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Anthracycline antibiotics, originally isolated from *Streptomyces peucetius* cultures, are effective against more types of cancer than any other class of chemotherapeutic agents currently available. Since their discovery in the 1960s, anthracyclines have been used extensively for the treatment of a wide range of childhood and adult cancers (1-3). The key mechanisms that mediate anticancer effects of this class of antibiotics include intercalation with DNA and inhibition of the DNA repair enzyme topoisomerase II, generation of intracellular reactive oxygen species, and resultant damage to cell membranes, proteins, and DNA that lead to cancer cell death (4). However, despite their potent anticancer effects, clinical use of anthracyclines is limited by their cardiotoxicity, which can manifest as irreversible myocardial damage, cardiac dysfunction, and heart failure (HF), a major cause for mortality in cancer survivors (5). Pre-existing cardiovascular risk factors can further predispose to chemotherapy-related cardiotoxicity, thereby limiting their use in cancer patients with cardiovascular comorbidities (6).

The propensity for cardiotoxicity varies with different cancer therapies, with the highest incidence observed in patients treated with anthracyclines, especially doxorubicin (DOX) (7). The mechanisms underlying anthracycline cardiotoxicity show considerable overlap with their anticancer effects and may involve multiple intracellular targets (1,8). The cardiotoxicity is dose-dependent (9). To date, there are limited strategies to minimize DOX cardiotoxicity that largely include minimizing the cumulative dose and modifying the dosing regimen (prolonged infusion, dose fractionation, liposomal delivery). A longitudinal study in survivors of childhood cancer showed that younger cancer patients were susceptible to DOX-cardiotoxicity, not only at higher doses but also at doses <300 mg/m^2. Furthermore, the resultant structural and functional changes persisted well after a decade of completion of treatment (10). These findings implied that cardiotoxicity is a continuum, with subclinical asymptomatic toxicity observed initially and exacerbation of cardiac structural and functional changes occurring with subsequent doses. Because of the increasing number of cancer diagnoses, improvement in cancer survival and long-term effects of cardiotoxicity on the quality of life, there is an urgent and yet unmet need for strategies that can protect the heart.

The key challenge in selecting a cardioprotective agent and optimizing the dose and timing of its administration is ensuring that it does not compromise the anticancer effect by targeting mechanisms common to cancer cell apoptosis and cardiac cytotoxicity. Dexrazoxane may be effective, but its use clinically has been limited (11,12). The availability of cardioprotective agents and HF treatments, including β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antioxidants, and diuretics, have been tested for their ability to limit or treat cardiotoxicity, but results do not yet support their routine clinical use (1,13,14).

A study by Gertz et al. (15) in this issue of *JACC: CardioOncology* explores the effect of remote ischemic pre-conditioning (RIPC) in a mouse model of DOX-induced cardiotoxicity. RIPC is a phenomenon in which short repeated cycles of sublethal ischemia–reperfusion (IR) in a vascular bed elicits

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protection against subsequent lethal IR injury (IRI) within the ischemic and remote nonischemic organs (16). Neurohumoral factors released into the circulation in response to RIPC are proposed to activate intracellular pro-survival pathways that inhibit mediators of IRI (17,18). RIPC is easily achieved by repeated inflation and deflation of a pneumatic blood pressure cuff placed around the limb. Several small animal and proof-of-concept Phase II clinical studies have shown robust cardioprotection with RIPC against IRI (19–21). However, recent reports from larger outcome clinical trials have failed to show a clinical benefit for RIPC in patients who have undergone elective cardiopulmonary bypass grafting and those presenting with ST-segment elevation myocardial infarction followed by primary percutaneous intervention (22,23). The lack of a beneficial effect in these studies were potentially due to several factors, including patient comorbidities and concurrent medications, all of which are known to modify the responsiveness to and/or efficacy of RIPC in this population (24).

SEE PAGE 221

Anthracycline cardiotoxicity and IRI activate several common signaling pathways and cytotoxic responses in cardiomyocytes (25,26). This has provided the basis for the ongoing ERIC-ONC (Effect of Remote Ischemic Conditioning in Oncology) clinical trial aimed at examining the effect of RIPC as a novel cardioprotective treatment in cancer patients receiving anthracyclines (27). In the study by Gertz et al. (15), mice subjected to RIPC 1 h before a bolus dose of DOX were shown to have significantly improved survival compared with the DOX-treated mice without RIPC pre-treatment. DOX treatment increased cardiac fibrosis and reduced left ventricular mass, both of which were attenuated by RIPC. Markers of apoptosis and autophagy were increased in response to DOX, whereas RIPC pre-treatment attenuated these changes. Surprisingly, DOX did not significantly affect mitochondrial dysfunction or reduce cardiac function. Nonetheless, based on these findings, the investigators concluded that RIPC might be an effective cardioprotective strategy to prevent DOX-induced cardiotoxicity. The RIPC protocol used was similar to that carried out in humans, and therefore, clinically feasible. Also, the salutary effects of RIPC on multiple known cellular targets of DOX was addressed, which lent further support to potential usefulness of RIPC in limiting cardiotoxicity.

The findings presented by Gertz et al. (15) open an exciting new avenue for cardioprotection using RIPC; however, there are caveats as discussed by the investigators. The use of healthy adult wild type mice and treatment with a single DOX dose limited extrapolation of the findings to the clinic. Studies using tumor-bearing animal models with cardiovascular risk factors are essential to examine if the cardiotoxicity-limiting effect of RIPC is preserved despite comorbidities and if RIPC modifies anticancer effects of DOX. Preliminary findings from cancer cell lines showed that simulated ischemic preconditioning did not abrogate the cytotoxic effects of DOX (28). Childhood cancer patients, who often present without cardiovascular morbidities, but yet are highly susceptible to cardiotoxicity, might represent the ideal patient group to benefit from RIPC cardioprotection. To facilitate this, more studies in young animals harboring DOX-responsive tumors are required. Furthermore, a multidose model of DOX administration may be clinically more relevant than bolus dose administration. Optimization of RIPC in a multidose DOX dosing model with tumors will require careful consideration of the following: 1) type and stage of cancer; 2) time course of the cardiac effects of these interventions; and 3) potential interactions among the underlying cellular mechanisms of cancer cytotoxicity, cardiotoxicity, and conditioning effects.

As a cardioprotective strategy, RIPC is inexpensive, noninvasive, non-pharmacological, easily administered, and lacking systemic adverse effects. If shown to be effective in limiting cardiotoxicity, this phenomenon could prevent the transition of patients from cancer survival to HF. This will ultimately improve accessibility of an effective chemotherapy regimen with better cancer and cardiac outcomes.

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