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EDITORIAL COMMENT

Remote Ischemic Conditioning for Anthracycline Cardiotoxicity

The Need to Protect the Most Vulnerable*

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The wide implementation of new and conventional anticancer therapies, increasingly as combination therapy, is significantly increasing the population of cancer survivors. However, this population is especially vulnerable to cardiovascular disease. In fact, noncancer deaths become increasingly important in oncology patients, particularly after surviving the first years postdiagnosis, with the main cause of death cardiovascular in specific cancer- and age- subgroups.[1] Cancer therapies may also be an important contributor to long-term cardiovascular complications.

Among the many anticancer therapies, anthracyclines remain one of the most commonly used[2] and form an essential component of curative regimens for many cancers, including breast cancer, sarcoma, acute leukemias, and lymphomas.[3] Appropriate dosing may determine the curative potential of these regimens.[4] One of the well-known side effects of anthracyclines is heart failure (secondary to direct cardiotoxicity of these agents). There is a clear association between the cumulative dose of anthracyclines and future development of cardiac dysfunction and heart failure. Although the mechanisms of anthracycline-cardiotoxicity are not completely understood, mitochondrial damage,[5] damage to the cardiac microcirculation,[6] and DNA damage[7] have been implicated.

The issue of anthracycline cardiotoxicity is of particular concern in pediatric and elderly patients, given the impact of age extremes on the risk of cardiac dysfunction after anthracycline exposure. For instance, the growing population of long-term survivors of acute lymphoblastic leukemia, the most common pediatric cancer, still experience late mortality and morbidity. Significant cardiovascular conditions, including heart failure, are increased in this setting, compromising duration and quality of life after cancer cure.[8] In adults, diffuse large B-cell lymphoma accounts for the majority of non-Hodgkin lymphomas and increases in incidence with age. The disease is curable in most patients if conventional, anthracycline-containing regimens (R-CHOP [rituximab, cyclophosphamide, doxorubicin hydrochloride] or similar) can be administered,[9] but may be especially difficult to treat in the elderly, where concerns for cardiovascular toxicity negatively impact the prescription of effective regimens.[10] Given the current prolonged life expectancy of these malignancies,[11] and the increasing therapeutic options at relapse, preservation of an adequate cardiac function is crucial to allow cancer therapies to be delivered safely.

The search for an intervention that can protect the heart against anthracycline-cardiotoxicity has been the matter of intense experimental and clinical research.[12] Several interventions have been tested with disparate results. Most of the trials performed so far have the common limitation of small sample size. Beta-blockers, renin-angiotensin-aldosterone system inhibitors, and statins are among the most frequently tested therapies.[13] However, results from these trials have been inconsistent. Importantly, with few exceptions,[14] patients enrolled in these trials are mostly "all-comers" and not enriched for characteristics associated with high-risk of cardiotoxicity.

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Remote ischemic (pre)conditioning (RIC) is an intervention consisting of brief episodes of ischemia followed by reperfusion (induced by a blood pressure cuff) in an organ (usually arm or leg) with the aim of conferring protection to remote organs such as the heart, brain, kidney, etc. Via this intervention, distant organs may receive signals to "prepare" them for a subsequent insult (eg, infarction). In some models, the final damage has been limited by RIC.[15] This intervention has been tested extensively in fields such as myocardial infarction and stroke, but the need to be applied before the index injury has limited its effective clinical application in many scenarios. Anthracycline cardiotoxicity may be an ideal scenario for RIC to exert beneficial effects because the cardiac insult (anthracycline administration) is scheduled, and RIC can be delivered before each chemotherapy cycle. The most robust demonstration of the cardioprotective potential of RIC against anthracycline cardiotoxicity has come from a highly translatable pig model, where RIC was demonstrated to induce remarkable protection and prevention of decline in cardiac systolic function.[16]

In this issue of *JACC: CardioOncology*, the first 2 (pilot) randomized clinical trials testing RIC as a preventive intervention for anthracycline cardiotoxicity are reported. Mallouppas et al[17] present the results of the ERIC-Onc (Effect of Remote Ischaemic Conditioning in Oncology Patients) trial, in which 55 adult patients (mean age 49 years) with any cancer scheduled to receive anthracyclines were randomized to RIC (4 cycles of 5-minute arm ischemia followed by 5-minute reperfusion) or sham before each chemotherapy cycle. Mean cumulative anthracycline dose was relatively high (317 mg/m^2). The primary endpoint, circulating levels of cardiac troponin (cTn), was not different between groups. The trial was underpowered for the primary outcome because the trial was stopped early due to the COVID-19 pandemic. It is noteworthy that at 3 months, there were virtually no changes in either left ventricular (LV) ejection fraction (LVEF) between groups (62% to 58% in RIC vs 60% to 59% in sham) nor in LV global longitudinal strain (−19% to −18% vs −19% to −18%).

In a separate trial also published in this issue *JACC: CardioOncology*, Cheung et al[18] tested the effects of RIC in a pediatric population of 68 patients (mean age 11 years) with different cancers. They were randomized to RIC (3 cycles of 5-minute arm ischemia followed by 5-minute reperfusion) or sham before each chemotherapy cycle.[18] The mean cumulative dose of anthracycline was low (155 to 157 mg/m^2). The primary endpoint, also circulating levels of cTn, was not different between groups. LVEF assessed by echocardiography was not different between groups (65% at baseline and 62% at follow-up in the RIC group, and 67% at baseline and 66% at follow-up in the sham group). LV strain was not substantially changed in either group (−16% to −15% in RIC, and −16% to −16% in sham).

We thus face the first 2 clinical trials, one in adults and another in pediatrics, testing the cardioprotective effects of RIC against anthracycline cardiotoxicity, and both appear neutral. Before reaching conclusions, there are important aspects that need to be taken into consideration. First, both trials have small sample sizes, and therefore, they should be considered as pilot studies. Secondly, the prevalence of anthracycline cardiotoxicity was extremelly low in both trials. It is noteworthy that there was no sign of LV function deterioration in either. The lack of decline in LVEF or impairment in strain suggests that in this trial population, anthracyclines did not seem to induce significant cardiotoxicity, thus limiting the ability to demonstrate the cardioprotective potential of any intervention. These results raise the question of whether future trials should move away from an "all-comers" design and enroll only those patients who are at increased risk for developing anthracycline cardiotoxicity, who are in greater need of cardioprotective interventions. Besides lifetime cumulative dose, there are other known risk factors for anthracycline cardiotoxicity, including hypertension, coronary artery disease, obesity, diabetes, age >65 years, abnormal baseline LV systolic function, and others.[19] The 2 trials discussed here enrolled populations that did not seem to be at particularly high risk for cardiotoxicity. In the trial by Mallouppas et al,[17] although the cumulative dose was relatively high, patients did not have other high-risk features (eg, only 9% had hypertension, 4% diabetes, and mean age was <50 years). In the trial by Cheung et al,[18] the cumulative dose was relatively low, and no other risk factors were present. Another very relevant aspect is the primary endpoint chosen in both studies: cTn levels. Although there were elevations in troponins in both groups, these were modest, and the mechanistic and prognostic relevance of this rise is unclear. Endpoints based on cardiac function and the dichotomization of patients into the absence or presence of cardiotoxicity based on recent clinical practice guidelines criteria[19] may be better suited for testing cardioprotective interventions in this field, even if this is at the cost of requiring larger sample

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sizes. For example, a LVEF reduction by ≥10 percentage points to an LVEF <50% would arguably be a more clinically relevant outcome to be included in future trials.

One aspect that needs to be clarified is the safety of RIC in the context of cancer treatment. Although experimental data suggest that RIC does not confer protection to cancer cells (probably the opposite), this outcome is of such a clinical relevance that it deserves special attention. In the trial by Mallouppas et al,[17] there were more cancer deaths in the group of patients undergoing RIC. However, it is important to note that at baseline, 54% of RIC patients had metastatic disease compared with 37% in the sham group. Furthermore, relapsed cancer patients were also more prevalent in the RIC group at the time of study enrollment (25% vs 19%), producing a significant imbalance in disease severity at randomization. This imbalance likely accounted for more cancer deaths in the RIC group up to 12 months postchemotherapy.

The most obvious question is whether there is a basis for further investigation of RIC as an intervention to prevent anthracycline cardiotoxicity. The significant cardioprotective effects in large animal models of anthracycline cardiotoxicity,[16] and the protection observed in other clinical scenarios[20,21] represent a strong premise to continue testing this non-invasive, cost effective, and easily implementable therapy. In this regard, the largest trial in the field of cardio-oncology, RESILIENCE (REmote iSchemic condItioning in Lymphoma PatIents REceiving ANthraCyclinEs; NCT05223413), is in progress across 5 European countries. This trial, funded by the European Commission, will enroll a total of 608 patients with lymphoma, and the inclusion criteria enrich the population for those at higher risk of cardiotoxicity. Patients are randomized to weekly RIC (4 × 5-minute cycles) or sham during the period on chemotherapy (approximately 4 months) and undergo comprehensive magnetic resonance imaging at baseline, half-way through chemotherapy, and 9 weeks after anticancer treatment completion. Until results of the RESILIENCE trial are reported, RIC should remain a highly promising intervention for preventing anthracycline cardiotoxicity.

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