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EDITORIAL COMMENT

Preventing Cancer Therapy–Related Cardiotoxicity

Should We be PROACTive or Reactive?

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Treatment with cancer therapy and, more recently, immunotherapy has transformed the prognosis for many patients diagnosed with cancer. Nowadays, approximately 50% of patients with a diagnosis of cancer survive for more than 10 years.[1,2] However, these advances in treatment have been paralleled by the downside of the "collateral damage" of cancer therapies, including the potential development of cardiotoxicity and ultimately heart failure.[3] For cancer survivors, cancer therapy–related cardiac dysfunction (CTRCD) is a serious concern, impacting upon both quality and quantity of life. Once cardiac dysfunction is established, prompt initiation of guideline-directed medical therapy is recommended.[3,4] However, preventing the cardiovascular damage is more desirable.

To date, several studies have investigated the role of conventional heart failure medications in preventing CTRCD.[5] In this issue of *JACC: CardioOncology*, Austin et al[5] report the results of the PROACT (Preventing Cardiac Damage in Patients Treated for Breast Cancer and Lymphoma) trial, an open-label, randomized clinical trial in 111 patients with breast cancer or non-Hodgkin lymphoma scheduled to receive anthracycline therapy. In this trial, comparing the renin-angiotensin-system inhibitor (RASi) enalapril to standard of care during chemotherapy did not prevent the incidence of CTRCD, defined as a rise in troponin >14 ng/mL over the course of anticancer treatment.

The results of this trial are concordant with most of the evidence in this area. For patients undergoing chemotherapy, treatment with RASi does not prevent the occurrence of CTRCD.[6] After 1 of the earliest trials showing a significant reduction of cardiotoxicity in patients treated with anthracycline after initiation of RASi,[7] no other trial has demonstrated a beneficial effect of this treatment.[6]

However, the hope that we can prevent cardiotoxicity should not be abandoned. It is important to consider this trial further to avoid its misinterpretation. The first important point to focus on is the definition of CTRCD. The recent guidelines on cardio-oncology divide CTRCD into asymptomatic and symptomatic; both groups are then subdivided into different categories according to the severity.[3] Recently, the International Cardio-Oncology Society (IC-OS) and the Heart Failure Association (HFA) have developed a risk score, the HFA-IC-OS score, to aid risk stratification.[8] In this trial, approximately one-half of the patients were in the low-risk category, and only a minority in the higher groups. This may have partially affected the results and underscores the need for risk stratification at baseline. For studies investigating prevention of clinical events, a higher-risk population may be needed to achieve the minimum number of events necessary to provide a clearer answer.

Interestingly, although the trial was deemed underpowered due to difficulties in recruitment, the final incidence of CTRCD was higher than expected. This highlights the fact that it is important to discriminate between what is clinically observable from what is clinically relevant. A mild rise in serum troponin concentration may not invariably lead to adverse events during follow-up. Therefore, the effect of medical therapy, in this case of RASi, might be diluted. To corroborate this point, the secondary

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endpoints in this trial were not changed by the introduction of enalapril. Neither left ventricular ejection fraction nor global longitudinal strain were significantly affected by enalapril. However, longer follow-up duration may be needed to observe changes cardiac function, which may occur further downstream.

Over the last decades, cancer treatment has also evolved significantly. For breast cancer, high-dose anthracyclines are less commonly used, due to combination therapy and the use of novel agents. Thus, the incidence of CTRCD may be lower.

The risk of CTRCD may also vary with genetics. In patients with unrecognized rare variants for dilated cardiomyopathy, cancer therapy may play a synergistic second-hit role for the development of clinically overt CTRCD.[9-11] In this group of patients, the incidence of CTRCD may be higher, and preventive measures could have a different result.

Altogether, the results of this trial strengthen the evidence available on the use of RASi for the prevention of CTRCD. When considering preventive treatments for patients undergoing anti-cancer therapies, it is important to discern whether we should be proactive, that is, give a treatment to a large population of asymptomatic patients to reduce a possible future event or be reactive and treat mainly patients at a higher risk of CTRCD. The latter strategy requires better risk stratification and the identification of novel markers of early cardiotoxicity. It also requires more studies to provide us with novel approaches so that we can target the correct medication for the correct patients at the correct time.

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