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EDITORIAL COMMENT

Natriuretic Peptides and Troponins

Sufficient Monitoring of Cancer Survivors?*

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Adequate and continuous monitoring of childhood cancer survivors for heart failure and other cardiovascular adverse events is crucial for an early detection of cardiovascular disease. Despite the remarkable progress made in treating childhood cancers, the therapies employed (particularly anthracyclines and radiation therapy) can inadvertently inflict damage on the entire cardiovascular system, predisposing survivors to an increased risk of, eg, heart failure, coronary artery disease, valvular heart disease, hypertension, and arrhythmia later in life.[1] Heart failure, a more commonly encountered long-term adverse event, is often linked to an inferior prognosis and quality of life, and contributes to a significant portion of premature deaths among cancer survivors. Moreover, the evaluation of a patient's risk for enduring cardiac complications from cancer treatments is contingent upon factors such as lifestyle choices and individual circumstances.[2] These aspects underscore the importance of personalized assessments in predicting and managing long-term cardiotoxic effects in cancer survivors.

Programs aimed at long-term cardiac surveillance for individuals who have undergone therapy as children or adolescents need to established protocols for the early detection of adverse events. Given that cardiac complications may manifest early after therapy or years and decades after treatment completion, it is recommended to conduct vigilant cardiovascular monitoring for asymptomatic patients for many years.[3] As time progresses, the frequency of echocardiography may be reduced (compared to monitoring during therapy) to alleviate concerns regarding excessive monitoring. A comprehensive examination is crucial, because echocardiography is adept at detecting diastolic dysfunction, valvular heart disease, or elevated pulmonary arterial pressure, alongside reduced left ventricular function (LVEF). Although strain analysis (global longitudinal strain [GLS]) holds promise as a prospectively ascertained routine echocardiographic parameter, its incorporation currently warrants individual consideration, particularly in longitudinal follow-up. In cases where sonographic limitations are encountered, cardiac magnetic resonance imaging serves as a viable alternative to echocardiography. Although the identification of reduced LVEF should prompt initiation of heart failure therapy even in asymptomatic patients, the clinical significance of cardiac magnetic resonance imaging findings such as late gadolinium enhancement necessitates further clarification.[4] Similarly, the prognostic relevance of biomarkers in asymptomatic long-term cancer survivors remains inadequately understood,[5] warranting additional research before implementation in routine heart failure screening. In the event of heart failure detection, treatment should adhere to current guideline recommendations, given the absence of tailored heart failure therapy recommendations specifically for long-term cancer survivors.

The prognostic value of troponins and natriuretic peptides (B-type natriuretic peptide [BNP]/N-terminal pro-B-type natriuretic peptide [NT-proBNP]) in chemotherapy-induced cardiotoxicity has previously been assessed for acute and chronic cancer therapy-related cardiac dysfunction. Both troponins and BNP/NT-proBNP may be released during cardiotoxic cancer therapy, and prior studies

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detail the use of these markers in the surveillance of cancer patients undergoing active cytotoxic or HER2+ targeted therapies or post-anthracycline therapy.[6,7] It should be noted, however, that the incidence of abnormal troponins is comparably rare in cancer survivors, and data regarding troponins' predictive value for manifest heart failure or mortality related to cardiotoxicity remain elusive.

In this issue of the *JACC: CardioOncology*, Leerink et al[8] aim to assess the diagnostic value of a combined biomarker approach in childhood cancer survivors. The authors used a specifically designed model to rule-out cancer therapy-related cardiac dysfunction in cancer survivors. Treatment regimens included anthracyclines and/or chest-directed radiotherapy. The multivariable logistic regression model included cardiac biomarkers (NT-proBNP and high-sensitive troponin T [hs-cTnT]) in combination with clinical characteristics in 1,334 patients of the Dutch late effects after childhood cancer (LATER) cardiology study (CARD). Clinical characteristics included sex, age at diagnosis, age at study, anthracycline dose, chest-directed radiotherapy dose, and heart rate. None of the included patients had a previously known diagnosis of cardiomyopathy. Reduction in LVEF below 50% was detected in 10.9% of the patients in the study.

The salient findings are as follows: 1) natriuretic peptides were abnormal in 22.1% of the patients at risk, whereas hs-cTnT above 10 ng/L was detectable in 5.8%; 2) a reduction in LVEF below 50% was ruled out in 16.9% with high sensitivity (95.4%) and negative predictive value; and 3) comparable results were achieved when attempting to rule-out an LVEF <45%.

The authors should be congratulated on this meticulously designed study with a prospective approach, encompassing a substantial cohort of childhood cancer survivors. LVEF measurements were conducted by an echocardiography core laboratory.

A few limitations of the study should be noted, however. First, the assessment of biomarkers must prompt a thorough investigation of the individual patient in case of pathological findings. This could relate to the potential diagnosis of coronary artery disease rather than heart failure in patients with elevated hs-cTnT. It is tempting to speculate that their combined model could also be used to rule out the sum of cancer therapy-related cardiovascular toxicity rather than LVEF reduction alone. Second, the median age was approximately 34 years for cancer survivors and 36.8 years in siblings. Although abnormal findings of natriuretic peptides and troponins are uncommon in these patients, the use of this model for older populations of cancer survivors remains less certain. Third, 17% of the patients had missing LVEF by echocardiography. Finally, the current focus of cardio-oncology survivorship programs is the timely (particularly subclinical) detection of cancer therapy-related cardiac dysfunction. The authors argue that their model showed good sensitivity and negative predictive value for an impaired LVEF. Arguably a reduction in LVEF already signals a severe impact on the heart. GLS may be more accurate for the detection of early adverse events. A validation of their findings against abnormal GLS, or even a combined diagnostic strategy incorporating biomarkers and imaging techniques, such as strain echocardiography,[9] would therefore be desirable.

In summary, the monitoring of childhood cancer survivors for heart failure remains a challenge for safeguarding their long-term well-being. By assessing cardiac health and implementing appropriate interventions, health care providers can significantly enhance the quality of life and overall outcomes for these individuals, facilitating a smooth transition into a healthy and fulfilling postcancer life.

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