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Need for Multidisciplinary Research and Data-Driven Guidelines for the Cardiovascular Care of Patients With Cancer

Wouter C. Meijers, MD, PhD, **Javid J. Moslehi, MD**

Cardio-oncology Program, Divisions of Cardiovascular Medicine and Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee.

Cardio-oncology has developed as a new field due to the proliferation of novel cancer therapies that not only have improved outcomes for some types of cancer, but also may lead to various cardiovascular toxicities.[1] Older therapies, such as anthracyclines, are associ- are associated with cardiomyopathy as a result of myocyte death at the time of treatment, followed by cardiac remodeling in the years following completion of therapy, and eventually lead to heart failure (HF). In 2019, data are limited on the prevention and treatment of cancer treatment-associated cardiomyopathy, with most interventions extrapolated from general HF clinical trials, which often exclude patients with cancer. Clinical studies are needed that focus on patients with cancer and cancer survivors with cardiovascular issues.

In this issue of *JAMA,* Singh et al[2] report the results of the MADIT-CHIC Study, in which 30 patients with chemotherapy- induced cardiomyopathy were treated with cardiac resynchronization therapy (CRT). The patient population enrolled in MADIT- CHIC was similar to patients included in larger trials of CRT in the general HF population, with patients having systolic cardiac dysfunction (as measured by left ventricular ejection fraction [LVEF] <35%), a wide QRS complex on the surface electrocardiogram, and HF symptoms (New York Heart Association class II-IV HF symptoms). The primary end point was a change in cardiac function (as measured by LVEF) 6 months after initiating CRT. Secondary outcomes included all-cause mortality and change in LV end- systolic and end-diastolic volumes. Among the 26 patients for whom follow-up data were available for the primary end point, patients with CRT had clinically significant improvement in LVEF (from 28% to 39%). For 23 patients, data on secondary outcomes were available: CRT was associated with improvements in LV geometry (reduction in LV end-systolic and end-diastolic volumes). There were no deaths and only 1 HF rehospitalization in the short follow-up of the study. These results are quite encouraging.

This preliminary study provides useful data to help better define cardiovascular care for patients with cancer. Most of the patients enrolled in the study were treated with anthracyclines, which are associated with dose-dependent cardiomyopathy. Because the development of anthracycline-associated cardiomyopathy often occurs years after exposure to treatment, the authors ruled out other causes for cardiomyopathy (eg, ischemia). The study contributes to the general acceptance in the cardiology community that cancer

Corresponding Author: Javid J. Moslehi, MD, Cardio-oncology Program, Vanderbilt University Medical Center, 2220 Pierce Ave, Nashville, TN 37232 (javid.moslehi@vanderbilt.edu).

survivors with symptomatic cardiomyopathy need to receive standard and guideline-directed therapy for HF much like other such patients without cancer.

The MADIT-CHIC Study has limitations. The findings should be considered preliminary because of the small size, short duration of follow-up, and lack of a control group. Because of the long period from the last cancer diagnosis (on average, 13.8 years), there are limited data with respect to the specific aspects of cancer therapy, such as dose of chemotherapy received and concomitant radiation. Additionally, the authors grouped the entire patient population into one category irrespective of cancer type or cancer therapy received. While most patients (83%) received anthracyclines, the details of the other cancer therapies and whether these agents may have been the cause of HF are less clear. Importantly, despite enrollment ofpatients from 12 tertiary centers with cardio-oncology programs and the 4-year duration of the study, only 30 patients were enrolled, and a smaller cohort had follow-up data. By comparison, the MADIT-CRT Study, another trial designed to determine the effect of CRT with biventricular pacing plus an implantable cardioverter-defibrillator-compared with implantable cardioverter defibrillator alone-on death or HF events in patients with mild cardiac symptoms, enrolled 1820 patients over a 4.5-year period. The study demonstrated clinical efficacy of CRT with a 41% relative reduction in HF events (absolute rates: 187/1089 [17.2%] in the CRT group and 185/731 [25.3%] in the control group) in a prespecified subgroup.[3]

The low patient enrollment by the MADIT- CHIC Study investigators raises an important question. Is cancer treatment- associated cardiovascular disease (CVD) less frequent than it is generally believed to be? This is unlikely. In 2019, there are an estimated 17 million cancer survivors in the United States, representing 5% of the total US population.[4] Irrespective of age, cancer survivors are at significantly increased risk of CVD including HF.[5,6] The risk of HF is particularly increased in patients exposed to anthracyclines, which remain the cornerstone of therapy for pediatric cancers, lymphoma, sarcoma, and a subset of breast cancers. While newer cancer therapies maybe less frequently associated with systolic HF, each can have other significant cardiovascular risks, including arrhythmia, vascular, or metabolic perturbations. In addition, immunotherapies can be associated with inflammatory heart disease, such as myocarditis.[1] This increase in risk of CVD in cancer survivors has been a driving force behind the establishment of cardio-oncology programs across the country.[7] Therefore, cancer survivors at risk of developing CVD represent a group of patients that is likely to increase in number.

The low enrollment in the study also suggests a need to identify and follow adult cancer survivors who received cardiotoxic therapies and who may be at risk of HF. This concept of closer monitoring has been introduced and implemented in the pediatric oncology population for whom multi-institutional and collaborative studies have resulted in data-driven guidelines and survivorship algorithms to help practicing clinicians longitudinally follow up patients (including with respect to cardiovascular dis- orders) in dedicated clinics.[8] More recent society statements, such as those by the American Society of Clinical Oncology and the National Cancer Center Network, propose cardiovascular risk assessment in adult cancer survivors exposed to anthracyclines.[9,10]

These recent initiatives by the adult oncology community are similar to the pediatric guidelines, but there is still one important distinction. Among pediatric patients exposed to anthracyclines, cardiac imaging, using echocardiography, is recommended following treatment with anthracyclines to identify patients with subclinical changes that can result in impairment of LV function (decreased LVEF as a measure of cardiac systolic function), which may lead to clinical HF.[11] Routine LVEF assessment following treatment with anthracyclines has not been generally accepted by the adult oncology community, representing an important difference in practice patterns among adult and pediatric oncologists. The argument has been that no randomized trials have been completed showing that routine echocardiography is effective in identifying and preventing cardiomyopathy in patients with cancer exposed to anthracyclines. On the other hand, cardiovascular imaging has been incorporated for detecting cardiotoxicity associated with other cancer therapies, such as trastuzumab inpatients with breast cancer. In addition, most patients undergo echocardiography prior to treatment with anthracyclines. Accordingly, studies are needed that address the utility of routine cardiac imaging following treatment with anthracyclines in adult patients.

While the adult oncology community has resisted routine assessment of LVEF following anthracycline treatment, several cardiology groups have advocated for even more advanced cardiac testing, often in the absence of conclusive data. For example, a statement from the American Society of Echocardiography suggests the use of global longitudinal strain (GLS), a quantitative evaluation of the mechanical deformation of the myocardium, measured with echocardiography, as an early measurement ofcar- diac dysfunction in patients treated with anthracyclines.[12] This recommendation lacks support from rigorous studies involving GLS in the cardio-oncology population, and a meta-analysis concluded that the “risk of bias in the original studies, publication bias, and limited data on the incremental value of GLS and its optimal cutoff values highlight the need for larger prospective multicenter studies.”[13] Another issue is efforts by the cardiovascular imaging community to seek reimbursement forthese modalities. As of2020, the Centers for Medicare & Medicaid Services will allow billing for GLS and other novel echocardiographic parameters, thus introducing a financial incentive for physicians to perform additional testing. Furthermore, studies are needed that introduce interventions that prevent or mitigate the development of cardiomyopathy in asymptomatic or high-risk adult patients.

The adult cardiology and oncology communities need a more harmonized approach to cardiovascular care ofpatients with cancer. Beyond rigorous clinical studies to clarify which cardiovascular testing should be incorporated, there is a growing need to bring a more personalized approach to patient care. Not all cancer survivors have the same risk of developing CVD and thus identifying those at risk should be a focus of future studies. Identifying high-risk patients can introduce a tailored approach, which might include imaging modalities, biomarker assessment, or both. Research agencies need to recognize these issues, especially by providing funding opportunities that call for multidisciplinary and multipronged approaches. Clinical data for the young field of cardio-oncology emerged from collaborations between pediatric oncologists and pediatric cardiologists, who helped define clinical characteristics of anthracycline-associated cardiotoxicity in children.[14] Larger multi-institutional databases, eg, the Childhood Cancer Survivor Study, have helped formulate

preventive and treatment strategies forthese patients.[5,15] Such approaches need to be applied to the increasing number of adult cancer survivors

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REFERENCES

1. Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies.NEngl JMed. 2016;375(15):1457–1467.
2. Singh JP, Solomon SD, Fradley MG, et al.; MADIT-CHIC Investigators. Association of cardiac resynchronization therapy with change in left ventricular ejection fraction in patients with chemotherapy-induced cardiomyopathy [published November 12, 2019]. JAMA. doi:10.1001/jama.2019.16658
3. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361(14):1329–1338. [PubMed: 19723701]
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7–34. [PubMed: 30620402]
5. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer.NEngl J Med. 2006;355(15):1572–1582.
6. Strongman H, Gadd S, Matthews A, et al.Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers. Lancet. 2019;394(10203):1041–1054. [PubMed: 31443926]
7. Hayek SS, Ganatra S, Lenneman C, et al. Preparing the cardiovascularworkforce to care for oncology patients. J AmColl Cardiol. 2019;73(17):2226–2235.
8. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors. J Clin Oncol. 2004;22(24):4979–4990. [PubMed: 15576413]
9. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers. J Clin Oncol. 2017;35 (8):893–911. [PubMed: 27918725]
10. Sanft T, Denlinger CS, Armenian S, et al. NCCN Guidelines Insights: Survivorship, Version 2.2019. J Natl Compr Canc Netw. 2019;17(7):784–794. [PubMed: 31319383]
11. Armenian SH, Hudson MM, Mulder RL, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer. Lancet Oncol. 2015;16(3):e123–e136. [PubMed: 25752563]
12. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy. J Am Soc Echocardiogr. 2014;27(9):911–939. [PubMed: 25172399]
13. Oikonomou EK, Kokkinidis DG, Kampaktsis PN, et al. Assessment of prognostic value of left ventricular global longitudinal strain for early prediction of chemotherapy-induced cardiotoxicity. JAMA Cardiol. doi:10.1001/jamacardio.2019.2952
14. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med. 1991;324(12):808–815. [PubMed: 1997853]
15. Lipshultz SE, Rifai N,Dalton VM, et al. The effect of dexrazoxane onmyocardial injury in doxorubicintreated children with acute lymphoblastic leukemia. NEngl J Med. 2004;351(2):145–153.