JACC: CARDIOONCOLOGY VOL. 4, NO. 3, 2022

EDITORIAL COMMENT

Consensus-Based Cardiomyopathy Care in Childhood Cancer Survivors

When You Don't Have a Roadmap, Ask Directions*

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Before there was a GPS-equipped smartphone in every pocket, one had to rely on printed roadmaps to go to unfamiliar destinations. However, those maps might be inaccurate as roads changed and as unsettled areas were developed. When a reliable map was not available for a given area, stopping and asking a local for directions was often the last resort. Sometimes this generated a confusing list of instructions, and other times, it revealed efficient information about unmapped discoveries on the way.

A common theme in the care of pediatric patients, particularly in cardiology, is that the extensive guidelines and evidence base that exist for adult patients is simply not available for children and adolescents. In addition, although adults who are childhood cancer survivors (CCS) may be covered by various published guidelines,[1-4] it is not clear whether simply applying these recommendations to pediatric, adolescent, and young adult patients is appropriate. What is more, there is limited guidance at all ages for the appropriate management of patients with asymptomatic or borderline left ventricular (LV) dysfunction. This is particularly important in CCS, because LV dysfunction and subsequent heart failure represent a significant proportion of the cardiotoxicity present.[5-7] Because the roadmaps to care for these patients are light on detail for the specific destination, practitioners often must "ask directions" on their journey.

In this issue of *JACC: CardioOncology*, Aziz-Bose et al[8] take an important step toward describing the real-world care of young CCS by presenting a Delphi study of 40 physicians from across the United States and Canada with recognized expertise in cancer survivorship from both pediatric and adult backgrounds. Participants responded to a survey with a variety of questions regarding screening and treatment for a hypothetical 20-year-old patient who received therapy for cancer at age 5.[8] Although patient demographics were vague, for example, sex and race were not specified, the investigators presented several clinical scenarios where different cardiotoxic treatments were provided. These included the use of specific anthracycline doses with and without dexrazoxane, and the inclusion of radiation therapy provided at different doses, sites, and modalities (photon vs proton). Medical experts were asked about the best options to screen for cardiomyopathy associated with the cancer therapies. In addition, medical experts were also questioned about the appropriate evaluation and treatment recommendations if patients had borderline LV systolic function, asymptomatic LV dysfunction, abnormal myocardial strain, or pregnancy.

Several interesting trends emerge in the paper, importantly the overarching theme that most of the scenarios in the survey are not explicitly covered in existing guidelines. For instance, data suggest that a significant number of young CCS experience borderline LV systolic function or asymptomatic mild LV dysfunction that may not cross the threshold for treatment in adult patients.[9,10] But in

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2022.08.001

a hypothetical 20-year-old patient treated for cancer as a child, over two-thirds of respondents indicated that they would start cardiac remodeling therapy in this setting, after reviewing this option with this patient ("shared decision-making"). Although this did not reach the level of "consensus" (≥90% agreement) or even "agreement" (75% to 89% agreement) set by the investigators, it gives an indication of real-world conundrums in treating these patients and identifies important research opportunities. In fact, the topics for which there was consensus or agreement were not surprising and, where appropriate, were in agreement with the available guidelines for this population.[11] These included use of echocardiogram as the standard screening modality for cardiomyopathy, referral to a cardiologist for abnormal LV function detected by echocardiogram, an indefinite duration of monitoring for anthracycline-induced cardiomyopathy, and use of standard cardiovascular laboratory assessment as additional screening tools. Although abnormal myocardial strain was accepted as an indication for referral to a cardiologist, there was also consensus that it should not be the sole indication for initiation of medical therapy. This is particularly interesting in light of the recent SUCCOUR (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes) trial and the debate that has arisen around application of the results.[12,13] Moreover, medical management issues commonly encountered in clinical practice caused disagreement in the study participants (<75% agreement), and firm recommendations were not provided. The need for screening in patients who received low-dose chest radiation therapy (<15 Gy), use of cardiac magnetic resonance imaging and stress testing as additional evaluation for cardiomyopathies, and when to start cardiac therapies were all topics of disagreement.

The study is not without limitations. Most notable, the recommendations included only met the level of expert opinion consensus met, and other than brief comments, it is not clear what specific data or evidence the respondents used to inform their decisions. This may certainly be an unavoidable limitation with the dearth of guidelines available for this patient population, but it would be informative to know which resources were important to the practitioners in specific scenarios. Regarding the profile of the 40 physicians who took the survey, it was at times too specialized, but also potentially not focused enough for certain circumstances. The panel did not represent several provider groups who routinely deal with these clinical matters in reality, such as nurse practitioners, community physicians, and those at smaller academic centers or regional hospitals. Moreover, the benefit of including 40 individuals was diminished when specific questions about the management of abnormal echocardiographic findings were posed, and only 14 participants were left to answer those questions. Nevertheless, we consider that the insight garnered by the work by Aziz-Bose et al[8] outweighs the limitations of this study.

The investigators make important strides to better understand how patients are followed and managed for borderline LV dysfunction and provide a set of recommendations for practitioners to use as a guide. With the difficulty in performing largescale treatment trials in this patient population due to relatively low numbers and ethical considerations of withholding standard therapy, similar expert opinion documents may be the best way to advance the field in the short-term. As to the clinical scenarios covered in future iterations of such work, expanding beyond traditional cardiotoxic therapies are crucial. Increasingly, young CCS have been exposed to nonanthracycline-cardiotoxic therapies, and, despite a known risk for cardiovascular disease,[14] there is nonexistent guidance for dealing with these patients. Next, because patients with cardiotoxicity are not specifically studied in drug trials, extending the survey to include patients with clinical heart failure and gathering opinions on new therapies (angiotensin receptor blocker-neprilysin inhibitor, SGLT2 inhibitors) would be of interest. A broader incorporation of "traditional" risk factors, and how they affect management, is needed in light of work done in large cohorts showing the effect on outcomes,[15] as well as incorporation of exercise testing and the utility of cardiac rehabilitation. Finally, insight into transition of patients from pediatric to adult care and who is best for managing patients is needed, as evidenced by differing opinions between pediatric- and adult-trained providers regarding indications for, and interpretation of, studies such as stress test and cardiac magnetic resonance imaging.

We may not yet have a detailed map of how to manage young CCS at risk for cardiomyopathy, but with the work presented by Aziz-Bose et al,[8] we have been given reliable directions by a local who knows the area, and as we explore new territory, we will contribute to the map that is being made and

JACC: CARDIOONCOLOGY, VOL. 4, NO. 3, 2022
SEPTEMBER 2022:368–370

updated in real time. And when the kids ask, "Are we there yet?" we can tell them that we are getting closer.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS anthracycline, cardiotoxicity, pediatric cancer, radiation, survivorship