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Research Paper

Overview of short and long-term management of cardiovascular disease in the cancer patient: Research-driven guidance for the clinician

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Cardio-Oncology is a pioneering new burgeoning field in cardiology. Cardio-oncology is defined as the intersection between cardiovascular disease and cancer; with a focus on mitigating cardiovascular disease risk factors [1]. Specifically, the aim of this field is the management and prevention of cardiovascular disease related to cancer treatment. The concept that cancer therapy, namely anthracyclines, cause cardiac dysfunction originated over forty years ago [2]. Previous research in this field has significantly expanded our understanding of cardiac disease related to cancer therapies. This field is a multispecialty collaboration that requires multimodalities and innovation; and can include initial cardiotoxicity risk mitigation, monitoring, and disease management. Many important studies have been published to help guide this field, and this is the time to hone what we have learned to generate more research to improve the care of cancer patients with heart disease. There is substantial room for growth in this field as new programs emerge and we learn more about cardiac disease mechanisms. This understanding can permeate our overall understanding of cardiac disease and lead to a new frontier of heart disease management and therapies.

The initial portion of the cardio-oncology practice model starts prior to cancer therapy. Prior to cancer therapy, an initial patient evaluation for the cardio-oncologist can include assessing patients' risk of cancer therapy-related cardiovascular disease. A detailed cardiac history can be helpful, and a cardio-oncology referral can be considered if patients have an extensive history. For the initial visit, Bhatia et al. [3] recommend an "ABCDE" method which includes identifying methods to mitigate cardiovascular disease (CVD) risk by treating high blood pressure and elevated cholesterol. This method also includes encouraging lifestyle changes related to a healthier diet, physical activity, and, if needed, promoting weight loss. During this visit, a surveillance plan can be generated based on known cardiotoxicity risk of the planned cancer therapy. A cardio-oncology referral can be considered, if a patient is at increased risk for cardiovascular (CV) complications due to prior CV or cancer treatment history, CV risk factors, or upcoming cancer treatments with high risk for cardiotoxicity.

During cancer therapy, the literature supports ongoing clinical and biomarker assessment, and cardiac imaging surveillance to identify incident cardiotoxicity [4,5]. For example, breast cancer patients have been the primary focus of the field due to the use of anthracyclines and trastuzumab. These cancer therapies can lead to heart failure. Anthracyclines bind to topoisomerase II beta (Top2β) to induce cancer cell death; however, Top2β is expressed in cardiomyocytes which can cause cardiac cell death and subsequently cardiac dysfunction [6]. Further, trastuzumab causes cardiac dysfunction by inducing cardiomyocyte apoptosis via its inhibition of the human epidermal growth factor receptor 2 (HER2) [7]. Breast cancer patients undergoing treatment with potential for cardiotoxicity such as anthracyclines or trastuzumab undergo a baseline and then serial evaluation of LV function, typically with 2-D echo (Simpsons biplane method), global longitudinal strain (GLS), 3-D when available, and occasionally cardiac MRI if echo data is suboptimal or inaccurate [8]. Global longitudinal strain (GLS) is typically recommended for these patients, and a 15 % decline in GLS can indicate subclinical left ventricular dysfunction [9]. For those patients with significant GLS decline, the patient-provider can consider cardioprotective medications (e.g., lisinopril and carvedilol) [10,11]. The important observational study SAFE-HEaRt has shown that breast cancer patients undergoing trastuzumab therapy with LVEF as low as 40 % can continue treatment with the use of cardioprotective medications [12]. If the LVEF borders on this threshold, cardiac magnetic resonance (CMR) can be considered for a more accurate assessment of the LVEF if it is borderline [8]. Different cancer therapies are associated with different forms of

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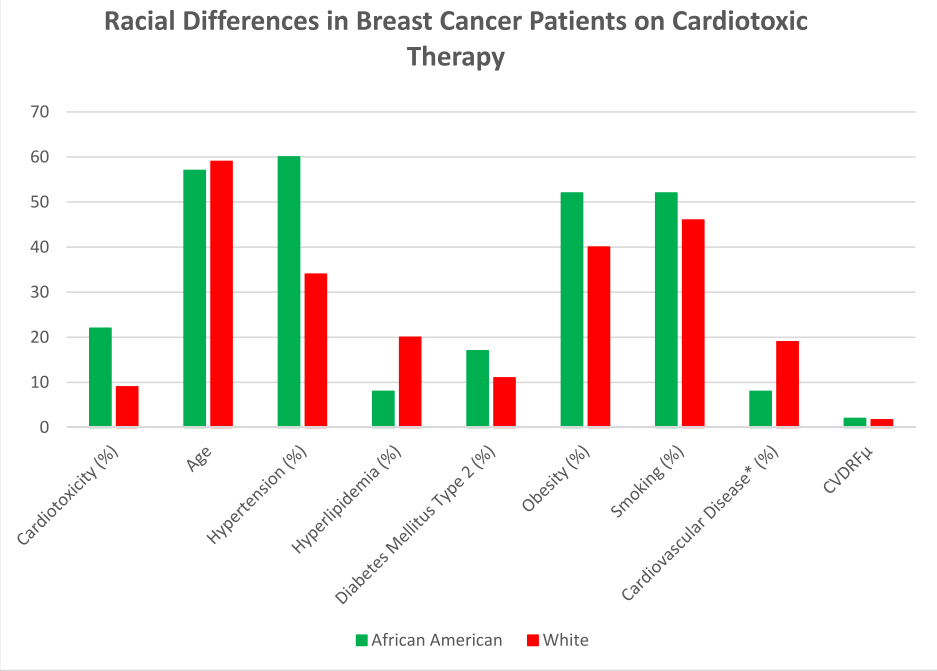

Fig. 14. Data from an observational study evaluating breast cancer patients exposed to anthracyclines and trastuzumab at Wake Forest Baptist Hospital. Demographics and clinical cardiovascular risk factors and cardiotoxicity incidence in African American patients compared with Whites. μCardiovascular Disease Risk Factors (CVDRF), *Cardiovascular Disease includes myocardial infarction, coronary artery disease, and stroke/transient ischemic attack.

cardiotoxicity such as tyrosine kinase induced hypertension, chimeric antigen receptor T-cells (CAR-T) associated arrhythmias, and coronary vasospasm related to 5-FU [13–19]. Using recommended algorithms can be helpful with the management of these patients based on the known cardiotoxicity associated with them [13]. The overall goal of management is to continue life-saving cancer therapy for as long as possible and cease therapy only if serious adverse cardiac events have occurred.

Finally, survivorship is an important component of the cardio-oncology practice model. For patients who are in remission there are still risks of cardiac effects of cancer therapies. Most notably one important aspect of survivorship care is surveillance for radiation-induced valvular fibrosis and accelerated atherosclerosis [20]. Valvular disease in particular is typically latent extending up to 20 years depending on the location of radiation and dose [18]. Radiation oncologists are more aware of this risk and new technologies are utilized to prevent radiation-induced cardiac disease [20]. Additionally, cardiovascular risk factors are highly prevalent in cancer patients and it is still important to be aggressive about mitigating CVD risk [21,22].

The cardio-oncology community and the American Heart Association (AHA) have collectively determined that the future for research in this field should include a focus on health equity. This is a widespread issue in cardiology in general, and cardio-oncology can set new precedents on addressing it. There is a consistent three-fold increased risk of cardiac dysfunction related to breast cancer therapy in African Americans compared to Caucasians [23–25]. The cause is multifactorial and requires further research. Hypertension (HTN) is a comorbidity prevalent in this population and can contribute to indirect causes of cardiac dysfunction [26–30] (Fig. 14).

Further contributions include a possible link to impaired nitric oxide synthesis and cardiotoxicity [31,32]. Importantly, social determinants of health, including racism, cultural habits (diet and physical activity), and access to centralized healthcare, contribute further to these disparities. Future research can focus on a better understanding of the causes and concrete solutions (e.g., more community clinics, telehealth). This integrative field benefits from a multidisciplinary framework that includes cardio-oncologists and oncologists. Establishing practices requires consistent communication between specialties and ideally opportunities to discuss complex cases during cancer board sessions. In the end, these and other proposed solutions may help improve access to care for all cancer patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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