Diagnosis and Management of Cancer in Children

Subjects: Cardiac & Cardiovascular Systems

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It is disheartening for parents to discover that their children have long-term cardiac dysfunction after being cured of life-threatening childhood cancers. As the number of childhood cancer survivors increases, early and late oncology-therapy-related cardiovascular complications continue to rise. It is essential to understand that cardiotoxicity in childhood cancer survivors is persistent and progressive. A child's cancer experience extends throughout his or her lifetime, and ongoing care for long-term survivors is recognized as an essential part of the cancer care continuum. Initially, there was a lack of recognition of late cardiotoxicities related to cancer therapy. In 1984, pioneers like Dr. Lipshultz and others published anecdotal case reports of late cardiotoxicities in children and adolescents exposed to chemotherapy, including some who ended up with heart transplantation. At that time, cardiac tests for cancer survivors were denied by insurance companies because they did not meet appropriate use criteria. Since then, cardio-oncology has been an emerging field of cardiology that focuses on the early detection of cancer therapy-related cardiac dysfunction occurring during and after oncological treatment.

cardio-oncology cardiotoxicity cancer-therapy related cardiotoxicity oncological cardiomyopathy

1. Diagnosis and Risk Stratification

Identifying high-risk patients and diagnosing cardiotoxicity early in children before symptoms of HF occur requires a careful assessment of CV risk factors before, during, and after cancer therapy with standard history, physical examination, clinical and laboratory tests for cardiac biomarkers, and imaging methods. The risk of cardiotoxicity depends on the patient's cancer diagnosis, the treatment received, and adverse health behaviors such as tobacco smoking, drinking alcohol, drug use (e.g., cocaine, diet pills, ephedra, mahuang), poor dietary habits, sedentary lifestyles and comorbidities such as pre-existing cardiomyopathy and underlying congenital heart disease, hypertension, hyperlipidemia, diabetes, and obesity [1]. The Childhood Cancer Survivor Study and other studies identified factors that increase the risk of developing cardiac toxicity, including younger patient age (<5 years), African American race, female sex, trisomy 21, total anthracycline dose, concomitant radiation exposure, underlying heart disease, pre-modern radiation protocols (before 1975), and time since treatment [2]. Furthermore, there is evidence that subclinical cardiac damage in cancer patients exists even before cancer therapy, which emphasizes the need to evaluate cardiac status in patients before cancer therapy [3]. Most of the existing guidelines regarding monitoring for the development of cancer-therapy-related cardiac dysfunction (CTRCD) are established for adult patients, with limited discussion of adult survivors of pediatric cancer [4][5][6]. Pediatric patients

who receive anthracyclines >400 mg/m^2 will develop restrictive cardiac dysfunction 30 to 40 years after cancer therapy. This long gap is an essential drawback in following these patients for late CTRCD because most patients attain adulthood. There is no continuity of care from pediatric to adult life, thinking that there are normal, and they lose contact with their pediatricians and pediatric oncologists.

1.1. Cardiac Biomarkers

Measuring serum cardiac biomarkers can be a useful diagnostic tool for baseline assessment, the diagnosis of sub-clinical CTRCD during and following treatment, identifying high-risk patients who benefit from cardioprotective therapy, and tailoring oncologic therapies to individual risk profiles [7]. Elevated cardiac troponin T and BNP or NT-pro-BNP levels identify subclinical cardiac injury in patients with cancer therapy without CAD and are associated with depressed LV function [8][9]. Myocardial injury (measured as serum cardiac troponin T ≥ 99th percentile) during anthracycline therapy is associated with lower LV mass, wall thickness, and echocardiographic remodeling five years later [10]. Also, abnormal NT-pro-BNP (cardiomyopathy, age > 1 yr abnormal if NT-pro-BNP ≥ 100 pg/mL; age < 1 yr abnormal if NT-pro-BNP ≥ 150 pg/mL) during the first 90 days of anthracycline therapy is significantly related to LV remodeling (thickness to dimension ratio) by echocardiogram four years later [10]. Thus, screening with serial biomarkers matters for secondary prevention and monitoring long-term CTRCD in childhood cancer survivors. Galectin-3 is a biomarker related to cardiac inflammation and fibrosis, whereas ST2 (also known as soluble interleukin-1 receptor-like 1) is elevated in cardiac remodeling [10][11]. In one study, elevations in myeloperoxidase have been shown to predict cardiotoxicity [12]. Recently, exosomes, a subgroup of extracellular vesicles modulating multiple pathophysiological processes, have been proven to be a valuable biomarker for Doxycycline-induced cardiotoxicity [13]. Standardizing routine biomarker use in this clinical setting for children receiving cancer therapy is urgently needed. Given the variability of chemotherapy schedules and the possible different release kinetics of various biomarkers, future research should clarify whether a multi-biomarker approach would permit better risk stratification for CTRCD.

1.2. Role of Echocardiography

1.2.1. 2D Echocardiography

Echocardiography plays a pivotal role in detecting structural changes such as diminished LV contractility expressed as LVEF, reduced LV wall thickness, and progressive LV dilation (increased LV end-diastolic diameter) even without symptoms. Patients should be stratified as having stage B HF if any changes are noted by echocardiography, according to the most recent 2022 ACC/AHA guidelines [14]. Early detection and prompt therapy of cardiotoxicity appear crucial for substantial recovery of cardiac function [15]. In adult cancer survivors, an absolute reduction in LVEF > 10% from baseline is described as CTRCD by the European Society of Cardiology (ESC), American Society of Echocardiography (ASE), American Society of Cardiac-Oncology (ASCO), and European Society for Medical Oncology (ESMO) [4][16][17]. Baseline echocardiography is essential to rule out pre-existing myocardial dysfunction, and those with normal LVEF should have a serial assessment by echocardiography during and after the completion of chemotherapy. However, 2D-derived LVEF has numerous limitations, such as preload and

afterload dependence. Because cancer patients receive varying amounts of intravenous fluid and constant changes in hemodynamic stressors occur, 2D-derived LVEF may not be sensitive or specific to predict risks for CTRCD [18]. Furthermore, LVEF measurement lacks reproducibility, and there is 10% inter- and intra-observer variability [19].

1.2.2. 3D Echocardiography

3D echocardiography has been reported to have superior reproducibility compared with 2D LVEF and lower inter- and intra-observer variability [19]. 3D LVEF changes also precede 2D LVEF changes [20][21], and 3D-derived LVEF correlates better with LV function estimated by cardiac magnetic resonance (CMR) [22]. 3D echocardiography-derived LVEF is likely to improve the accuracy and reproducibility of estimated LV function [23]. Serial 3D echocardiographic measurements of LVEF may be an early marker to detect subtle changes in LV function and thus can determine if a cardioprotective agent should be used along with anthracycline therapy. Although preferable to 2D, 3D echocardiography is restricted by limited availability in all centers, increased cost, and the need for an experienced operator to obtain high-quality images in children.

1.2.3. Speckle-Tracking Global Longitudinal Strain

The recent development of semi-automated myocardial strain imaging by speckle-tracking echocardiography (STE) provides a more sensitive and reproducible measurement of myocardial deformation by tracking speckle displacement during the cardiac cycle. Strain is expressed as a percentage corresponding with the deformation in a region of interest. Unlike the measurement of LVEF, the strain does not rely on volume overload, and strain imaging may permit early detection of subclinical cardiotoxicity [24]. Global longitudinal strain (GLS) is the most commonly used strain parameter to assess early regional LV function abnormalities and appears to be most suitable for monitoring serial changes [25]. According to ASE guidelines, GLS is determined as the average peak longitudinal strain of 17 LV segments from 3 standard apical views [26]. In adult cancer survivors, LV GLS falling below (−)18% (0% to −17.9%) or a > 15% relative decrease of this marker may suggest clinically significant cardiotoxicity [24]. Pre-treatment measurements of GLS in cancer patients were significantly lower in the CTRCD group than in the non-CTRCD group, which may indicate an increased baseline risk profile for cardiovascular disease. The study of Ali et al. supports this finding; their results demonstrated that reduced baseline GLS > −17.5% was a strong predictor of cardiac events in patients with hematologic cancers [27].

Studies have shown abnormal longitudinal and circumferential strain in anthracycline-treated childhood cancer survivors [28][29]. In adults, cardioprotective therapy guided by LV GLS is beneficial [30]. However, to date, no predictive data in children demonstrates that the early detection of cardiotoxicity by strain analysis will alter the clinical prognosis. Such data would facilitate the modification of chemotherapy and the introduction of therapy to minimize the impact of cardiotoxicity. Right ventricular (RV) strain parameters have recently been found to be a useful early marker for subclinical CTRCD [31]. Myocardial strain imaging is thus a promising clinical modality for early cardiotoxicity detection and long-term surveillance of cancer patients [32][33].

1.2.4. Tissue Doppler Imaging

Tissue Doppler imaging (TDI) or tissue velocity imaging has been used to evaluate diastolic dysfunction in children [34]. Rajapreyar et al. showed that diastolic dysfunction could be detected by TDI earlier than systolic dysfunction in children treated with anthracyclines [35]. However, the predictive value of LV diastolic impairment to predict CTRCD is doubtful because of inconsistent results regarding its ability to predict the subsequent occurrence of systolic dysfunction [36]. Additional clinical research and more extensive trials are necessary to evaluate the prognostic role of TDI parameters in childhood cancer survivors.

1.2.5. Role of the Stress Test and Stress-Echocardiography

Cardiopulmonary exercise testing (CPET) provides a simple, noninvasive method for assessing dyspnea by unmasking pathology that resting studies cannot elicit. In addition, it can screen for cardiac dysfunction and other causes of shortness of breath in patients receiving chemotherapy, such as pulmonary hypertension, evolving pneumonitis or fibrosis, mitochondrial myopathy, or deconditioning. For this reason, CPET studies may be the ideal first-line tool for the workup of subclinical cardiac dysfunction in childhood cancer survivors [37]. The role of stress echocardiography is potentially helpful in risk-stratifying patients undergoing cancer therapies associated with myocardial ischemia [38]. As such, dobutamine stress echocardiography is a sensitive method to detect subclinical and clinical cardiac dysfunction in long-term survivors of asymptomatic children treated with anthracycline chemotherapy [39][40].

1.3. Role of CMR

CMR is recommended in patients with poor-quality echocardiographic images and patients with pre-existing heart diseases (for example, hypertrophic or dilated cardiomyopathy) [41]. It has greater intra- and inter-observer reproducibility and may identify a higher prevalence of CTRCD compared to echocardiography [42]. CMR does not utilize ionizing radiation, has an excellent spatial resolution, and can provide detailed tissue characteristics, including myocardial edema, inflammation, and fibrosis, thus playing an essential role in the identification of early and late cardiotoxicity in patients after cancer therapy by use of late gadolinium enhancement (LGE) and quantitative mapping techniques (T1 and T2 mapping). CMR also accurately assesses RV function by quantifying RV end-diastolic and end-systolic volumes. Recent reports have demonstrated that CMR-derived LV strain allows the detection of subclinical LV dysfunction during and after potentially cardiotoxic cancer therapy [43]. A decreased LV mass index suggestive of myocardial atrophy or growth arrest is an independent predictor of cardiomyopathy in cancer patients treated with anthracyclines [44]. Also, children exposed to anthracyclines have been shown to have increased left atrial (LA) volume when measured by CMR [45]. The superior spatial resolution of CMR provides the additional benefit of obtaining LA strain throughout the cycle of LA emptying and offers excellent information on diastolic dysfunction in childhood cancer survivors [46].

1.4. Role of Cardiac Catheterization

Anticancer therapies can cause significant injury to the vasculature, resulting in angina, myocardial ischemia, stroke, arrhythmias, and HF, independently from the direct myocardial or pericardial damage that might occur. Moreover, cancer is generally associated with a hypercoagulable state, which increases the risk of acute

thrombotic events. Consequently, the need for invasive evaluation and management in the cardiac catheterization laboratory for adult cancer patients has been growing [47]. The role of cardiac catheterization in children receiving cancer therapy is limited except where angina or CAD is suspected.

1.5. Role of Advanced Imaging CT/SPECT/PET

The role of computed tomography (CT) is limited in pediatric cardio-oncology patients. CT coronary angiography may serve as an alternative imaging modality to stress echocardiography in a baseline assessment, though its higher cost and radiation exposure may limit its widespread use [48]. A common cardiovascular complication of cancer therapies is impairment of coronary circulation, either through direct vascular damage or accelerated atherosclerosis [49][50]. Noninvasive methods for evaluating myocardial perfusion with such parameters as myocardial blood flow and coronary flow reserve quantification are desirable in cardio-oncology care. For years, single-photon electron computed tomography (SPECT) imaging has been one of the principal methods for evaluating flow-limiting coronary stenosis in cardio-oncology patients, with the most commonly used radiotracers being 99mTc-labeled Sestamibi and Tetrofosmin. A large adult study that monitored cardiac function using serial SPECT over seven years and involved nearly 1500 patients who received cumulative doxorubicin doses of ≥450 mg/m^2 showed that 19% of patients were at high risk of cardiotoxicity (defined as LVEF < 50%, a drop in LVEF by ≥10%) [51]. Although monitoring resting LVEF by SPECT helps detect early anthracycline cardiotoxicity, it has a low sensitivity compared to advanced imaging such as positron emission tomography (PET), especially with vectors labeled with positron-emitting radionuclides (e.g., carbon-11, fluorine-18, gallium-68) [52]. Cardiac PET is the current gold standard to assess myocardial perfusion because of its higher spatiotemporal resolution, count sensitivity, and accuracy. It is also valuable for diagnosing coronary microvascular dysfunction, especially with chemotherapy like Cyclophosphamide and 5-FU in adults [53]. Furthermore, PET allows for the evaluation of myocardial viability [54]. Despite these advancements, a lack of validation in the pediatric population has limited the use of PET imaging techniques in pediatric cardio-oncology patients. Limited data regarding optimal thresholds to distinguish pathologic from normal hyperemic myocardial blood flow and coronary flow reserve are available in children.

2. Management

It is important to note that there is a variation in the definition of CTRCD across national societal position statements and oncology trials in adults [6][7][55][56]. Also, rates of cardiotoxicity and HF among children differ from those in adults with different anticancer agents. Hence, a standard recommendation will not fit children and adults to guide prevention, monitoring, and treatment strategies. Nonetheless, a multidisciplinary team, including cardiologists, oncologists, and allied healthcare professionals, must consider multifactorial risk factors for each patient receiving cancer therapy. In particular, the pediatric cardiologist should inform the oncologist of the patient's cardiovascular risk factors, pre-existing cardiac disease status, prognosis, and intended treatment plan.

2.1. Prevention

Prevention can be primary and applicable to all patients receiving cancer therapy with potential cardiotoxicity. Primary prevention aims to optimize pre-existing modifiable CV risk factors, including controlling high blood pressure, lowering cholesterol, maintaining a healthy blood glucose level, consuming a nutritious diet, and stopping smoking during and after cancer treatment. Moderate aerobic exercise in selected patients is a promising nonpharmacological strategy to decrease CTRCD [57]. A review of 56 studies involving 4826 participants showed improved quality of life and physical capacity during and after a physical training program [58]. Secondary prevention is identifying high-risk patients for the development of HF who show signs of early cardiac injury so that they can be monitored very closely and cardioprotective therapy can be initiated. [6]. Other secondary preventive strategies include reducing the anthracycline dose, administering anthracycline as a continuous infusion instead of a bolus, choosing liposomal formulations of anthracyclines, and using fewer cardiotoxic anthracycline analogs (Epirubicin, Idarubicin, and Mitoxantrone) [59]. Dexrazoxane is the only drug approved by the US Food and Drug Administration (FDA) for the secondary prevention of anthracycline-related cardiomyopathy. Dexrazoxane is an iron-chelating agent with documented cardioprotective effects [60][61]. Although it was initially thought that the cardioprotective effect of Dexrazoxane was related to its iron-chelating properties, leading to cytosolic iron sequestration, more recent evidence suggests that inhibition of Doxorubicin-topoisomerase complex formation, leading to a reduction of free radicals, may also play a role [62]. Dexrazoxane decreases the cardiotoxic effects of anthracyclines without reducing their anticancer efficacy [63]. Unlike in adults, where Dexrazoxane is delayed until the anthracycline dose is 300 mg/m^2, in children, it is recommended to give Dexrazoxane with the first anthracycline dose to be effective and to minimize cardiotoxicity in high-risk patients. Cardiomyopathy surveillance in cancer survivors for late CTRCD is recommended in all patients who received a total anthracycline dose of ≥250 mg/m^2 or an RT dose ≥ 35 Gy [5]. Cardiomyopathy surveillance in cancer survivors is reasonable if treated with a moderate dose of anthracycline (>100 mg/m^2 and <250 mg/m^2) or RT (>15 Gy to <35 Gy) [5]. Cardiomyopathy surveillance may be reasonable for survivors who received a total anthracycline dose <100 mg/m^2 [5]. An echocardiogram is a primary modality for surveillance to determine LVEF, either by 2D or 3D echocardiography [5]. Strain analysis to determine GLS is recommended but not widely used in children yet. CMR and other advanced modes of imaging are indicated only in selected patients.

The rationale for using standard HF medications such as angiotensin-converting enzyme (ACE) inhibitors and β-blockers is primarily extrapolated from the adult experience with limited pediatric data [14][64]. In 2006, Cardinale et al. demonstrated that ACE inhibitors and β-blockers were beneficial in adults with anthracycline-related cardiomyopathy if therapy is initiated soon after diagnosing LV dysfunction [15]. In another randomized trial to study the long-term cardiotoxicity of childhood cancer survivors, asymptomatic cancer survivors with preserved EF received either Enalapril or placebo [65]. The study found that patients treated with high-dose (300 mg/m^2) anthracyclines derived the most benefit from Enalapril therapy—six out of seven cardiac events occurred in the placebo arm, and nearly all were among those treated with high-dose anthracyclines. As a result, while using Enalapril to mitigate or prevent the cardiotoxic effects of cancer therapy may appear intuitive [66][67][68], the long-term impacts of containing HF have been disappointing. A multicenter, double-blind, randomized trial (NCT02717507) is currently ongoing to evaluate the long-term efficacy of Carvedilol in preventing cardiomyopathy and/or HF in high-risk childhood cancer survivors exposed to high-dose anthracyclines [69]. The study results will be

available after three years of follow-up. The result will provide much-needed information regarding pharmacological risk-reduction strategies for childhood cancer survivors at high risk for developing anthracycline-related HF.

Exercise is beneficial in certain groups of individuals but could be detrimental to a subgroup of survivors with restrictive physiology because unsupervised exercise can put them at risk for pulmonary congestion and arrhythmia [70]. For patient safety, individual exercise prescriptions based on the late effects of the individual patient should be developed rather than a group recommendation for all cancer survivors. They should be individually reevaluated over time since survivor health changes over time. Appropriate and safe increases in physical activity will decrease the survivor's cardiovascular risks, improve mental health, and decrease adverse cardiometabolic effects. Statins may be cardioprotective by reducing oxidative stress and inflammation in patients with other cardiovascular risk factors, but the benefits and risks remain unclear in the absence of any long-term studies in childhood cancer survivors [71].

2.2. Treatment of HF

Children who develop HF during therapy or over the long term after cancer therapy should be treated according to guideline-directed medical treatment [72]. Starting therapy early after the development of ventricular dysfunction can improve systolic function in most patients [73]. Currently, a "multi-hit model," i.e., combination HF therapies, is preferred for treating HF [74]. Complex neurohormonal activation may occur as a response to myocardial injury and correlate with the severity of HF. These observations form the rationale for neurohormonal antagonists for treating HF with beta-adrenergic receptor blockers, ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists [72]. Unfortunately, Enalapril improved LV systolic function over six years but deteriorated 6 and 10 years after treatment [10]. This is because the primary defect was LV wall thinning, which continues to deteriorate, and thus the short-term improvement is mainly related to lowered diastolic blood pressure. As such, no long-term study has shown any beneficial effects of ACE inhibitors in childhood cancer survivors on improving quality of life, providing long-term benefits, or reducing progression to HF or death. Sacubitril and Valsartan combination therapy have improved LV function and cardiac biomarkers in adults with long-standing cardiotoxicity-induced HF [75][76]. Recently, newer HF therapies, such as sodium-glucose co-transporter-2 (SGLT2) inhibitors, have improved outcomes in adults with diabetes mellitus and cancers treated with anthracyclines [77]. Based on therapies of proven benefit in adult HF studies, these newer HF agents may be helpful in children with cancer therapy-induced refractory HF [74]. Refractory pediatric HF patients may need hospitalization and inotropic therapy. In some patients with end-stage HF, advanced HF therapies such as mechanical circulatory support (MCS) and heart transplantation can be successfully implemented [78]. Patients can be supported with MCS while undergoing cancer therapy and ultimately be bridged to heart transplantation [79][80]. However, a recent single institutional study reported a higher incidence of RV failure (4 out of 6 patients) while supported by a left ventricular assist device in children with cancer therapy-induced advanced HF [80].

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