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Cardiovascular diseases in survivors of childhood cancer

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Abstract
Over the past few decades, the diagnosis and management of children with various malignancies have improved tremendously. As a result, there are an increasing number of children who are long-term cancer survivors. With improved survival, however, has come an increased risk of treatment-related cardiovascular complications that can appear decades after treatment. These problems are serious enough that all caregivers of childhood cancer survivors, including oncologists, cardiologists, and other health care personnel, must pay close attention to the short- and long-term effects of chemotherapy and radiotherapy on these children. This review discusses the effects of treatment-related cardiovascular complications from anthracyclines and radiotherapy and the methods for preventing, screening, and treating these complications.

Keywords Cardiotoxicity · Survivorship · Chemotherapy · Radiotherapy · Cardio-oncology

1 Introduction

The number of people living in the USA beyond a cancer diagnosis was more than 15.5 million in 2016 and is projected to exceed 20 million by 2026 [1]. The mortality rate of survivors has declined from 6.3 per 100,000 populations in 1970 to 2.1 in 2011 [2]. The 5-year survival rate for all forms of pediatric malignancies increased from 58% for children diagnosed between 1975 and 1977 to 83% for children diagnosed between 2004 and 2010 [3]. Unfortunately, the same treatments that cure cancer often cause adverse effects in other organ systems, especially the cardiovascular system [4]. Survivors of cancer are significantly more likely than their siblings to suffer from congestive heart failure, myocardial infarction, pericardial disease, or valvar abnormalities [5]. Anthracycline-containing regimens and chest radiation exposure in particular have been associated with an increased risk for these cardiovascular complications [5–10]. In the 2017 St. Jude Lifetime Cohort Study, 99.9% of 5,054 childhood cancer survivors had a chronic health condition by the age of 50 years [2].

2 Anthrcycline-induced cardiotoxicity

Anthracyclines are still the chemotherapeutic drug class of choice for treating many cancers [11]. Clinically significant cardiotoxicity is a major limitation of this medication, and this has recently led to the use of lower doses in the treatment of childhood cancer [2, 12]. They exert their anti-cancer effect either by intercalating between base pairs of DNA and preventing malignant cell replication or by inhibiting topoisomerase II activity which then prevents the uncoiling process of DNA required for replication [13]. Anthracyclines enter the cell through passive diffusion and have the capacity to reach concentrations much higher than extracellular

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compartments, due to the presence of high concentrations of cardiolipin in cardiomyocytes and high affinity of this cardiolipin for anthracycline [14, 15]. Once inside, it leads to formation of complexes with iron and reduces the quinone moiety to subquinone. This leads to a cascade production of free radicals (ROS) causing deleterious effects on the cell and all its components, resulting in cell death. Other changes noticed in cardiomyocytes exposed to anthracycline include depleted cardiac stem cells [16], impaired DNA synthesis [17], impaired cell signaling that triggers cell death [18], altered gene expression [19], inhibited calcium release from the sarcoplasmic reticulum [20], impaired formation of protein titin in sarcomeres [21], and impaired mitochondrial creatine kinase activity and function [22]. Over the last several years, there has been growing interest regarding topoisomerase-II β (Top2β) alterations being the mechanism of doxorubicin-mediated cardiotoxicity [23, 24]. Zhang et al. showed that cardiomyocyte-specific deletion of Top2β protects cardiomyocytes from doxorubicin-induced DNA double-strand breaks and transcriptome changes in mice, resulting in defective mitochondria [23]. This study showed that deleting Top2β from cardiomyocytes prevented the development of anthracycline-induced cardiotoxicity in mice. Because not all children exposed to anthracyclines develop cardiac abnormalities and the clinical severity of such abnormalities varies greatly, determining the factors that may increase susceptibility to these cardiotoxic effects is of great importance.

3 Risk factors and genetic determinants of cardiotoxicity

There is a strong and well-documented dose-dependent association between total cumulative exposure to anthracyclines (e.g., doxorubicin and daunorubicin) normalized by body surface area and the risk for anthracycline-related cardiomyopathy [2, 25–28]. In children, current protocols for the treatment of lymphomas, leukemias, and solid tumors include total cumulative doses of anthracyclines ranging from 75 mg/m^2 (e.g., acute lymphoblastic leukemia) to 450 mg/m^2 (e.g., osteosarcomas). These upper dose limits are based on estimates derived from group averages and do not account for individual differences in terms of susceptibility to cardiac damage. In 1974, Rinehart et al. noted that imposition of the 550 mg/m^2 upper dosage limit for Adriamycin (doxorubicin) in the context of therapies for various cancers ignores biological variation. This is relevant because such dosage limits may deny the drug to patients who could tolerate additional therapy or it may trigger cardiotoxicity at lower doses in susceptible individuals [29]. For example, it is known that some patients have tolerated cumulative doses in excess of 1000 mg/m^2, whereas others have experienced significant decreases in left ventricular ejection fraction and signs of cardiac toxicity after receiving relatively "low" cumulative doses of around 150 mg/m^2 [30–33].

The individual risk of cardiotoxicity results from complex interplays between patient- and treatment-related factors. For example, a pivotal retrospective study from the Pediatric Oncology Group (POG) based on the analysis of over 6,400 cases of pediatric cancers treated with anthracyclines per POG protocols concluded that female sex, African ancestry, presence of trisomy 21, and treatment with amsacrine increase the risk for anthracycline-cardiotoxicity [27]. Other recognized risk factors for cardiotoxicity include young age (< 4 years of age at diagnosis of primary cancer), chest radiation, and cardiovascular risk factors (e.g., diabetes, hypertension, obesity) [4]. However, these data have not been helpful for selecting appropriate doses of anthracyclines for individual patients. In this context, it has been postulated that a fraction of the variability in cardiomyopathy risk may be attributable to the presence of polymorphic variation in genes linked to the complex pharmacodynamics of anthracyclines. This notion helped propel the search for pharmacogenetic determinants of anthracycline-cardiotoxicity in diverse therapeutic settings.

The earliest study exploring the pharmacogenetics of anthracycline-cardiotoxicity was published in 2005 by Wojnowski et al. [34]. The authors showed that variants in genes encoding the multienzyme NAD(P)H oxidase complex (e.g., *NCF4*, *CYBA*, and *RAC2*) and the doxorubicin efflux transporters MRP1 and MRP2 were associated with the risk of cardiotoxicity in patients with non-Hodgkin lymphoma [34]. Since then, over 35 studies have explored the pharmacogenetics of anthracycline-cardiotoxicity in adult and pediatric cancer patients. These genetic association studies can be separated into two broad categories, candidate gene studies and genome-wide association studies (GWAS). Systematic comparisons between studies are difficult because there is substantial heterogeneity in terms of sample sizes, definitions of cardiotoxicity, therapeutic settings (e.g., types of cancer, age groups, treatment protocols), length of follow-up, lack of replication, functional validation of genetic variants, and other potentially relevant clinical and demographic variables. Recent reviews on the pharmacogenetics of anthracycline-cardiotoxicity include two systematic reviews by Leong et al. and Linschoten et al. [35–39]. The analysis by Aminkeng et al. concluded that pharmacogenomic testing for variants in *RARG* (rs2229774), *SLC28A3* (rs7853758), and *UGT1A6*4* (rs17863783) is recommended in childhood cancer patients with an indication for doxorubicin or daunorubicin therapy. In agreement, Linschoten et al. concluded that genetic variants in *RARG* (rs2229774) and *SLC28A3* (rs7853758) together with a variant in *CELF4* (rs1786814) are supported by relatively robust evidence in the context of therapy for childhood cancers [35].

Studies from the Children's Oncology Group (COG) have pinpointed polymorphic variants that appear to modify the

risk of anthracycline-cardiotoxicity in a dose-dependent context. For example, a nested case-control pilot study of patients enrolled in the Childhood Cancer Survivor Study (30 cases of anthracycline-related congestive heart failure (HF) and 115 matched controls) identified a trend toward a positive relationship between *CBR3* V244M (rs1056892) genotype status and the risk for anthracycline-related HF (odds ratio {OR} = 8.16 and $p = .056$ for GG vs. AA; OR = 5.44 and $p = .092$ for GA vs. AA). Consistent with these observations, kinetics studies of recombinant isoforms of CBR3 showed that CBR3 V244 (G allele) catalyzed the synthesis of doxorubicinol at 2.6 times the rate catalyzed by CBR3 M244 [40]. A second and larger study examined a cohort of 170 survivors with cardiomyopathy (patient cases) and 317 survivors with no cardiomyopathy (controls; matched on cancer diagnosis, year of diagnosis, length of follow-up, and race/ethnicity) [41]. In patients with *CBR3* GG, exposure to anthracyclines at a dose of 1–250 mg/m^2 increased cardiomyopathy risk when compared to individuals with *CBR3* GA/AA genotypes unexposed to anthracyclines (OR = 5.5, $p = 0.003$), or exposed to < 250 mg/m^2 (OR = 3.3, $p = 0.006$). This finding suggests that there is no safe dose of anthracyclines for individuals homozygous for the *CBR3* G allele [41]. A study by Minotti et al. based on human myocardial strips further highlighted the notion that modulation of the risk of cardiotoxicity by *CBR3* V244M may be dependent upon the type of anthracycline substrate [42]. In 2016, the same group of COG investigators reported results from a GWAS in survivors of childhood cancers (162 cases of cardiomyopathy and 268 controls in the discovery cohort) that uncovered a significant genome-environment interaction with a polymorphic variant in *CELF4* (rs1786814) [43]. Among those individuals exposed to > 250 mg/m^2 anthracyclines, rs1786814 GG genotype conferred a 10.2-fold (95% CI, 3.8–27.3, $p < 0.0001$) increased risk of cardiomyopathy compared with those with GA/AA genotypes and anthracycline dose ≤ 250 mg/m^2. This finding was replicated in an independent set of 54 cases with anthracycline cardiomyopathy. CELF proteins control the alternative splicing of *TNNT2*, the gene encoding for cardiac troponin T (cTnT). Coexistence of >1 cTnT variants results in a temporally split myofilament response to calcium, causing decreased contractility, and co-existence of ≥ 2 *TNNT2* splicing variants has been documented in cases of idiopathic dilated cardiomyopathy. Healthy human hearts with *CELF4* GG genotype were more likely to show coexistence of > 1 *TNNT2* splicing variants (GG: 90.5% vs. GA/AA: 41.7%; $p = 0.005$), suggesting that the association of polymorphic *CELF4* with the risk of anthracycline-cardiotoxicity may be mediated through the expression of abnormally spliced *TNNT2* variants [43].

Lipshultz et al. studied the C282Y and H63D mutations of the hemochromatosis gene (HFE), which is associated with hereditary hemochromatosis [44]. Since anthracyclines bind to iron in the blood to form free radicals, which injure or kill cardiomyocytes, they hypothesized that children with higher iron levels, such as those with HFE gene mutations, may have higher myocardiocyte injury. In 184 survivors of childhood acute lymphoblastic leukemia, after controlling for dexrazoxane treatment, 10% of patients heterozygous for C282Y had nearly a 9-fold increased incidence of elevated cTnT concentrations, suggesting myocardial injury, compared to those without this HFE gene mutation. Those patients with C282Y mutations had significantly more abnormal LV structure and function by echocardiography 2 years later than those without this HFE mutation.

Anthracycline-cardiotoxicity is a complex "pharmaco-phenotype" resulting from multiple patient- and treatment-related factors, and no single genetic variant will explain the total clinical risk for all patients across different and complex therapeutic scenarios [37–39]. There is a need for robust clinical algorithms in both pediatric and adult cancer settings to predict the individual's risk of anthracycline-related cardiomyopathy [28, 37, 45–47]. Identification of newly diagnosed patients with cancer at increased risk for developing cardiomyopathy would allow for therapeutic modifications or targeted use of cardioprotection (e.g., dexrazoxane). The identification of cancer survivors at increased risk for cardiomyopathy would also allow health care providers to (1) increase the intensity of screening for early detection of clinical signs and/or symptoms of cardiac damage and (2) institute targeted risk reduction strategies (behavioral interventions: physical activity, diet; pharmacologic interventions: e.g., beta blockers, anti-hypertensives) [48, 49]. Exciting progress is already being made in this area. For example, a new anthracycline-cardiomyopathy risk prediction model developed by COG investigators incorporates genotypic data from selected variants (e.g., rs1786814, rs4673, rs2232228) and clinical and demographic variables (e.g., age at cancer, cumulative anthracycline dose, chest radiation, and diabetes status) [50]. The model was able to identify childhood cancer survivors at high and low risk of anthracycline-cardiomyopathy. This integrative model provides the necessary platform for the development of robust prediction models to inform clinical interventions in childhood cancer survivors [50].

4 Diagnosis of anthracycline-induced cardiotoxicity

Anthracycline cardiotoxicity can be categorized at the time of presentation as either acute or chronic, with chronic cases further categorized as early- or late-onset [51] (Table 1). Acute toxicity may manifest within a week of treatment; early-onset cardiomyopathy, within a year of treatment or late-onset cardiomyopathy presenting at least 1 year after therapy [2, 14, 27, 30, 51–53]. Late-onset symptoms can also present in patients who do not

Table 1 Characteristics of the different types of anthracycline-associated cardiotoxicity

Characteristic	Acute cardiotoxicity	Early-onset, chronic progressive cardiotoxicity	Late-onset, chronic progressive cardiotoxicity
Onset	Within the first week of anthracycline treatment	< 1 year after the completion of anthracycline therapy	> 1 year after the completion of anthracycline therapy
Risk factor dependence	Unknown	Yes	Yes
Clinical features in adults	Transient depression of myocardial contractility; myocardial necrosis (cTnT elevation); arrhythmia	Dilated cardiomyopathy; arrhythmia	Dilated cardiomyopathy; arrhythmia
Clinical features in children	Transient depression of myocardial contractility; myocardial necrosis (cTnT elevation); arrhythmia	Restrictive cardiomyopathy and/or dilated cardiomyopathy; arrhythmia	Restrictive cardiomyopathy and/or dilated cardiomyopathy; arrhythmia
Course	Usually reversible on discontinuation of anthracycline	Can be progressive	Can be progressive

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necessarily show the first two types of cardiotoxicities [54]. Acute toxicity presents during treatment in less than 1% patients [14, 27, 51] and often manifests as arrhythmias, EKG abnormalities, HF, or as a myocarditis-pericarditis syndrome [14, 27, 51, 55]. Early-onset cardiomyopathy may show LV dysfunction, EKG changes, and/or clinical heart failure [2, 14, 27, 30, 51, 53]. According to a study in 2005, these patients initially develop a dilated cardiomyopathy with signs of reduced LV shortening and contractility along with LV dilation. Slowly, with time, it changes to a pattern of restrictive cardiomyopathy with normal to reduced LV dimensions along with significantly reduced LV wall thickness, fractional shortening, and contractility [54]. In late-onset cardiomyopathy, ventricular function deteriorates and often shows loss of cardiomyocytes, LV wall thinning, and sometimes, LV dilation [25, 26, 56]. Echo findings may include LV fractional shortening, decreased LV mass, LV contractility, and LV end-diastolic posterior wall thickness along with increased LV afterload [14]. A long-term follow-up of 115 survivors showed a decrease in the LV dimension to body surface area with subsequent increase in the LV thickness to body surface area resulting in normal LV thickness-to-dimension ratio, indicating ventricular remodeling. This shrinking myocardial cavity size for body surface area (which we refer to as "Grinch syndrome") is the chronic cardiomyopathy, which may result in HF, heart transplantation, or death among long-term cancer survivors [57]. The various stages of ventricular dysfunction are depicted in Fig. 1.

5 Prevention strategies for anthracycline cardiotoxicity

Given that currently available medical interventions do little to stop or slow the progression of treatment-related cardiotoxicity, efforts to prevent this toxicity remain of great clinical interest [58]. While some prevention methods have not proven as successful as hoped, the cardioprotectant dexrazoxane and several other strategies continue to hold great promise in helping prevent the occurrence of anthracycline cardiotoxicity [58, 59]. Dexrazoxane binds iron before it enters cardiomyocytes [60, 61], which prevents the formation of the iron-anthracycline complex and thereby prevents free radical release and subsequent cardiac damage. In addition, dexrazoxane can change the configuration of topoisomerase 2β, preventing anthracyclines from binding to it [62], further preventing cardiomyocyte death, mitochondrial dysfunction, and the supression of antioxidant gene expression [63]. Dexrazoxane has already been shown to reduce acute cardiotoxicity in adults receiving anthracyclines and is currently recommended by the American Society of Clinical Oncology for the prevention of cardiotoxicity in specific adult cancer treatment protocols [58]. A randomized controlled trial of dexrazoxane in children with acute lymphoblastic leukemia treated with doxorubicin showed that significantly fewer of the 82 children who received doxorubicin and dexrazoxane together had elevations in cTnT compared with the 76 children who received doxorubicin alone [64]. Dexrazoxane is the only agent approved by the United States Food and Drug Administration (FDA) to prevent anthracycline-induced cardiotoxicity [65]. In July 2017, the European Medicines Agency (EMA) overturned an earlier decision that now allows dexrazoxane to be given to children and adolescents treated with high cumulative doses of anthracyclines (> 300 mg/m^2 of body surface area) [66, 67]. This change in labeling was followed by a review by the EMA that is posted and updated on its website [66, 68]. This decision allows virtually all children to receive dexrazoxane starting with the first dose of anthracycline at the discretion of the treating provider [66].

Neurohormonal antagonists are routinely used in adults with HF, and are now being increasingly used—without

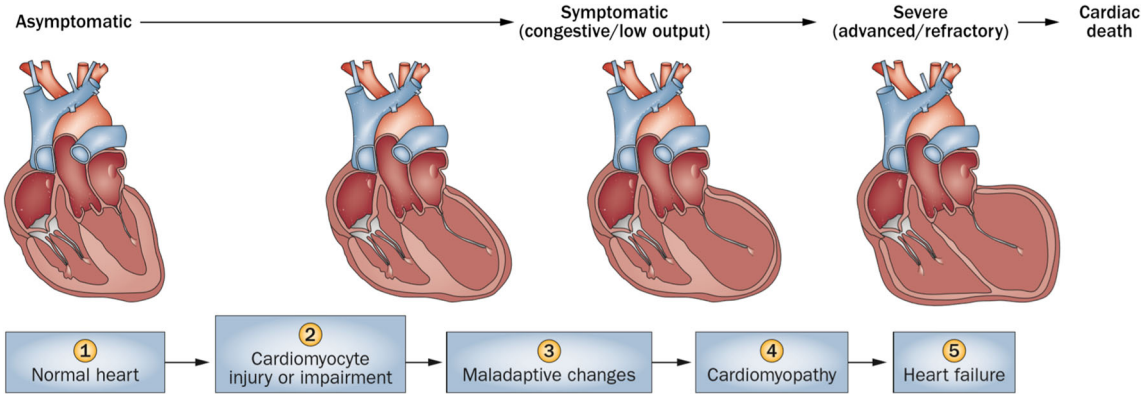

Fig. 1 Stages in the development of pediatric ventricular dysfunction (Reprinted with permission from Lipshultz SE, Cochran TR, Franco VI, Miller TL. Treatment-related cardiotoxicity in survivors of childhood cancer. Nat Rev Clin Oncol 10(12):697-710).

strong evidence—in the fragile population of childhood and adult cancer survivors for preventing or reducing the progression of cardiotoxicity [69, 70]. The literature specific to using these medications to prevent anthracycline-associated LV dysfunction in both adults and children is limited [71]. Most studies have a small number of subjects and short follow-ups, with some of the longest being just 12 months after completing therapy. Few studies have reported clinical events as a primary outcome and instead used subclinical measures, albeit markers validated in the general population. Thus, the "success" of the primary prevention studies is unclear [70–72]. Some of the trials lacked rigorously defined clinical endpoints or used endpoints that combined subclinical findings and clinical events [70, 71].

Future directions for cardioprotection in pediatric malignancies may include techniques to decrease total cumulative anthracycline dose and radiation exposure, as well as to develop alternative therapies that may eliminate the use of anthracyclines and radiation altogether in some cases.

6 Cardiotoxicity secondary to radiation therapy

Irradiation of the heart during cancer treatment can lead a wide spectrum of cardiovascular abnormalities in childhood cancer survivors. Cardiotoxicity can present acutely during radiotherapy for cancer treatment, potentially limiting dose and reducing the effectiveness of treatment, or decades after treatment, leading to early mortality due to accelerated treatment-induced heart disease. According to the American Society of Clinical Oncology, cardiovascular complications tend to develop in 10–30% of patients receiving radiation therapy usually after a mean follow up of 5 to 10 years [73].

The earlier detection and treatment of breast, lung, and mediastinal cancers with ionizing radiation have increased the proportion of cancer survivors [74, 75]. With millions of patients surviving cancer over the last decades, the effectiveness of radiotherapy in controlling the growth of tumors is raising hope for patients with aggressive and life-threatening malignancies [1, 76]. Thoracic radiation exposure increases the risk of cardiovascular disease characterized by causing structural and functional abnormalities of coronary arteries, valves, pericardium, and myocardium. The incidence of major coronary events increases linearly with the mean cardiac radiation dose, leading to a 7.4% increase per Gy in breast cancer patients who received tangential fractionated irradiation [77], a 33% increase per Gy in lung cancer patients treated with radiotherapy [78], and an increase of 1.5 to 3-fold after mediastinal radiation [79]. Unfortunately, the only available clinical solution to prevent radiation-induced organ damage is "dose reduction," which is not always possible without compromising its anti-cancer efficacy. A large proportion of patients with thoracic cancers, including those of the lung, esophagus, and stomach, receive considerable radiation doses [80, 81], increasing the risk for cardiovascular injury. Despite increased morbidity and mortality associated with radiation-induced cardiovascular disease, no specific therapeutic agents have been made available to-date to prevent or mitigate these conditions.

Cardiac fibrosis is a major factor contributing to myocardial remodeling in patients exposed to radiation [82, 83], and these patients have greater morbidity and mortality than those with HF from other causes. Radiation-induced fibrosis results from a complex interplay of multifactorial processes. Radiation exposure induces both acute and chronic changes in cardiac tissue. Within minutes of ionizing radiation, cellular injury causes damage to the endothelial cells. These cells secrete adhesion molecules and growth factors prompting activation of the acute inflammatory response. Recruited inflammatory cells secrete additional pro-inflammatory and pro-fibrotic cytokines including monocyte chemotactic factor; tumor necrosis factor (TNF); and interleukins (IL) including IL-1, IL-6, IL-8; platelet-derived growth factor (PDGF);

transforming growth factor β (TGF-β); basic fibroblast growth factor (bFGF); insulin-like growth factor (IGF); and connective tissue growth factor (CTGF) [84–86]. The acute phase lasts for several days after radiation exposure. Following this acute phase, there exists a quiescent period where there are no obvious microscopic changes in the tissue [87]. However, the acute inflammatory response triggers fibroblast recruitment, myofibroblast differentiation, and progressive fibrosis. Extracellular matrix deposition by fibroblasts results in dysfunction of myocardium, valves, and the pericardium.

Radiation can also cause both macrovascular and microvascular injury [88, 89]. For decades, studies have focused on macrovascular changes in epicardial coronary artery disease [90]. In contrast, little is known about the extent of ultrastructural and functional alterations in the myocardial pre-arterioles, arterioles, and capillaries after exposure. In a registry of 11,000 patients with a history of chest pain, 65% of women and 32% of men had no epicardial vascular obstruction, suggesting microvascular injury as a cause [91]. Microvascular injury affects the endothelial cells of small vessels and capillaries and can lead to myocardial ischemia and fibrosis [90, 92]. Radiation-induced ischemic heart disease can occur in the absence of significant atherosclerosis of the epicardial vessels [93]. These patients develop HF with preserved ejection fraction, which is the commonest manifestation of HF in patients with radiation exposure [94]. Risk factors that induce inflammation and oxidative stress may trigger endothelial dysfunction and alter the vasomotor function of the microcirculation [95]. With the development of modern, high-resolution cardiac magnetic resonance (CMR) technology, cardiac dysfunction can be identified by the assessment of coronary flow reserve [96]. To date, there are no known therapeutic agents that can specifically modulate this cardiotoxicity after cardiac irradiation.

The International Commission on Radiological Protection estimated a net 15-year loss of life expectancy in a population irradiated for cancer therapy [97]. Premature aging may have occurred, as cancer was found to have minimal effects on patient life spans. The complexity of premature aging lies in the fact that these effects appear after decades [98, 99]. Previously, it was believed that loss of organ function after radiation was a manifestation of direct organ damage, rather than aging [100]. Those theories were probably relevant to the cases that received single but high-dose radiation therapy leading to predictable deterministic effects [101]. The current radiotherapy protocols employ small but repetitive doses of radiation. Such low-dose protocols have greatly reduced the direct tissue damaging effects, but increase the chances of long-term stochastic effects [98]. Accelerated aging is potentially the most devastating consequence of such stochastic effects. Ionizing radiation is responsible for the accelerated senescent changes of cardiac conduction system leading to increased incidence of high-grade bradyarrhythmias [102, 103]. In addition, these patients have significant fibrotic and degenerative changes of the atria, ventricles, and valvular structures leading to impaired cardiomyocyte coupling and development of both supraventricular and ventricular arrhythmias.

There is increasing evidence that radiation exposure leads to endothelial cell senescence. Senescent endothelial cells exhibit reduced nitric oxide production and increased reactive oxygen species (ROS) release. This can lead to endothelial dysfunction including reduced vasodilator response and inhibition of angiogenesis. These effects can lead to radiation-induced target organ damage involving heart, lungs, and thoracic skin. Currently, there are no specific therapeutic agents available to counteract or mitigate endothelial senescence due to radiation exposure.

7 Prevention strategies of radiation-induced cardiotoxicity

Radiation therapy involves the use of high-energy particles, gamma rays, or X-rays which break down DNA and interfere with cell growth and proliferation. This affects both the cancer cells and normal tissue depending on tissue susceptibility and extent of radiation exposure. The most important means of prevention is reduction in radiation exposure [104]. Compared with current regimens, conventional regimens used larger total radiation doses and involved a wider area of irradiation. Intensity-modulated radiation therapy (IMRT) is an advanced mode of high-precision radiotherapy that uses 3D computer-controlled linear accelerators to deliver precise radiation doses to a tumor or specific areas within the tumor [105]. Proton beam therapy is an increasingly available radiation technique that can potentially spare neighboring critical structures more effectively than radiation using photons. Even with recent modifications of advanced radiotherapy techniques, risk of cardiovascular morbidity and mortality exists. It is therefore important to discover new ways of combating this problem.

While mechanisms contributing to cardiotoxicity for selected agents have been proposed, few have been explored in relation to radiation-induced cardiotoxicity during cancer treatment and survivorship care. Due to lack of mechanistic data, specific therapeutic agents have not been developed. Amifostine is a cytoprotective agent that appears to shield normal tissues from the toxic effects of chemotherapy and radiotherapy. It is a prodrug that is dephosphorylated by alkaline phosphatase to a pharmacologically active free thiol metabolite, which can act as a scavenger of free radicals generated in tissues exposed to radiation [106]. However, current guidelines do not advise the use of amifostine because of its higher side effect profile.

Statins, an inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, are used to treat hypercholesterolemia and have been reported to have some therapeutic potential as anti-inflammatory and anti-fibrotic agents [107]. The radioprotective effects of statins have been attributed to inhibition of several inflammatory kinases, including Rho and Rho-associated protein kinases, which regulate pro-inflammatory and pro-fibrotic stress responses, respectively [108, 109]. Additionally, pravastatin has been found to reduce radiation-induced cell death and attenuate radiation induced NF-κB, which is dependent on Rho family GTPases [105].

Ionizing radiation generates reactive oxygen species and disrupts essential macromolecules such as DNA and membrane lipids [110, 111]. Many antioxidants are undergoing study for prevention of radiation-induced cardiovascular disease. For example, melatonin has been reported as a scavenger of free radicals and also a potent antioxidant. In rat models following radiation, it has shown to reduce development of fibrosis, vasculitis, and myocyte necrosis. It has also been seen to attenuate radiation-induced cell death by upregulation of anti-apoptosis genes and inhibiting pro-apoptosis [112].

Previous studies from our group and others have demonstrated that Ac-SDKP exerts robust anti-inflammatory effects by inhibiting inflammatory cell infiltration, macrophage migration, and activation, thus inhibiting the release of pro-inflammatory and pro-fibrotic cytokines including transforming growth factor-β (TGF-β) and galectin-3 in the setting of cardiac dysfunction and remodeling [113–117]. Ac-SDKP is an endogenous peptide derived from thymosin-β4, which is present in most cells [118, 119]. Ac-SDKP also inhibits cardiac fibroblast proliferation and collagen synthesis *in vitro* [113].

8 Monitoring for cardiotoxicity

While there are several available techniques for monitoring the cardiac status of survivors before, during, and after cancer treatment, there is little evidence to guide their use [120]. Recognizing that childhood cancer survivors experience both short- and long-term cardiotoxic effects, the American Heart Association [121] and the Children's Oncology Group [122] have recommended that such children be regularly screened to detect early, subtle cardiac abnormalities that might be treated, or may be reversible [122, 123]. For patients who will be receiving known cardiotoxic therapies such as anthracyclines or ionizing radiation, baseline echocardiography and follow-up echocardiography that are focused on relevant cardiac data for the therapy employed can be helpful in identifying cardiotoxicity [124]. Nearly all treatment protocols including anthracyclines require a pre-treatment echocardiogram to ascertain baseline measurements of cardiac structure and function [124]. Various studies of children receiving anthracyclines found no relationship between echocardiographic measurements during treatment and serum levels of cTnT [125, 126]. However, current guidelines from the Children's Oncology Group recommend lifelong echocardiographic screening every 3 to 5 years in survivors treated with anthracyclines or cardiac radiation [122, 127]. Serial echocardiographic examinations are important for assessing cardiac anatomy, such as the pericardium, ventricular walls, and valves in patients treated with radiation. Particular attention must be paid to diastolic function because diastolic dysfunction is more likely to occur than systolic dysfunction in survivors treated with thoracic radiation therapy. Although, echocardiographic measurements of LV fractional shortening and ejection fraction continue to be the most widely used screening methods for monitoring cardiotoxicity, both during and after anthracycline treatment [124]. Biomarkers of cardiac toxicity (cardiac troponin T {cTnT}, cardiac troponin I {cTnI}, and N-terminal pro-brain natriuretic peptide {NT-proBNP}) are increasingly being used to monitor cancer survivors. One study showed that concentrations of these biomarkers were significantly higher in the doxorubicin-only treatment group than in the doxorubicin group pretreated before each dose with the cardioprotectant dexrazoxane group [128]. In this study, increases in blood cTnT concentrations during the first 90 days of doxorubicin therapy were associated with decreased LV mass and LV end-diastolic posterior wall thickness for body-surface area 4 years later, and increases in NT-proBNP concentrations during this same period were associated with changes in the LV thickness-to-dimension ratio, suggestive of pathologic LV remodeling [129, 130] (Fig. 2). Thus, these cardiac biomarkers have been validated as surrogate endpoints for cardiac effects of cardiotoxicity and should be utilized in future studies. Most recently, alterations in plasma microRNA expression in children receiving anthracycline or non-cardiotoxic chemotherapy were found to correlate with the microRNA expression of markers of cardiac damage (elevated cardiac troponin concentrations) and thus hold future promise as screening markers for therapy-associated cardiotoxicity [131].

9 Treatment of cardiotoxicity

Current screening recommendations led to the identification of a large and increasing number of asymptomatic and symptomatic cardiac complications [122]. According to the European Society of Medical Oncology Clinical Practice Guidelines Cardiac Review and Evaluation Committee [132], LV dysfunction is defined by a "(a) decrease in cardiac left ventricular ejection fraction (LVEF) that is either global or more severe in the septum; (b) symptoms of HF; (c) signs of HF, including but not limited to the presence of a S3 gallop, tachycardia, or both; and (d) a decline in LVEF of at least 5%

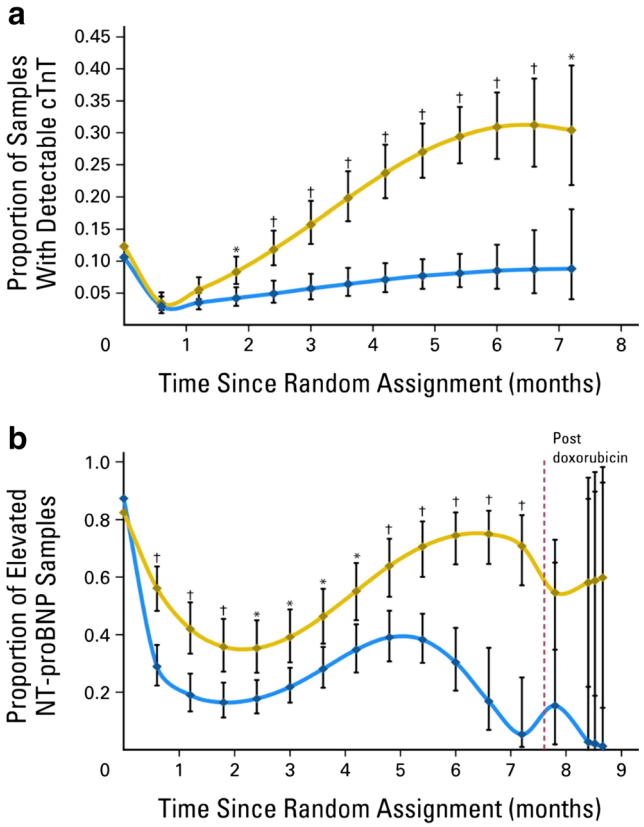

Fig. 2 Model-based estimated probability of having **a** an increased cardiac troponin T (cTnT) concentration or **b** an elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration in patients treated with doxorubicin, with or without dexrazoxane. The doxorubicin-dexrazoxane group is indicated by the blue line and the doxorubicin group by the gold line. Vertical bars show 95% confidence intervals. Increased cTnT is defined as a value greater than 0.01 ng/mL. *P vs. dexrazoxane group ≤ 0.05; †P vs. dexrazoxane group ≤ 0.001. An overall test for dexrazoxane effect during treatment was significant ($P < 0.001$). Increased NT-proBNP is defined as a value of 150 pg/mL or greater for children less than1 year old and 100 pg/mL or greater for children aged at least 1 year. *P vs. dexrazoxane group ≤ 0.05; †P vs. dexrazoxane group ≤ 0.001. An overall test for dexrazoxane effect during treatment was significant ($P < 0.001$) and after treatment was not significant ($P = 0.24$). (Reprinted with permission from American Society of Clinical Oncology Lipshultz SE, Miller TL, Scully RE, et al. Changes in cardiac biomarkers during doxorubicin treatment of pediatric patients with high-risk acute lymphoblastic leukemia: associations with long-term echocardiographic outcomes. J Clin Oncol. 2012 Apr 1;30(10):1042–9. [130])

to less than 55% with accompanying signs or symptoms of HF, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms." Currently, there is no standard therapy for chemotherapy or radiation therapy-induced cardiotoxicity and the goal of therapy is to prevent or slow LV remodeling rather than etiological treatment [133].

Angiotensin-converting enzyme (ACE) inhibitors and β-blockers are standard of care in adults with HF [134]. Thus, when cardiac dysfunction is observed in these patients, guideline directed medical therapy is often started. The use of these medications in patients with anthracycline-induced cardiomyopathy has been evaluated in limited settings in adults [71]. Even in pediatric cancer survivors, one study revealed transient improvement in the LV fractional shortening in 18 survivors treated with doxorubicin and the ACE-inhibitor, enalapril, for the first 6 years, which was followed by the progression of LV dysfunction between 6 and 10 years [135]. Additionally, in a randomized controlled trial in 135 long-term survivors of pediatric cancer, enalapril improved LV wall stress but did not improve exercise tolerance among patients [136]. A study in children with acute lymphoblastic leukemia receiving doxorubicin revealed that pre-treatment with carvedilol (a non-selective β-blocker and α-1 blocker) protected cardiomyocytes, as indicated by the inhibition of doxorubicin-induced increases in blood lactate dehydrogenase and troponin I concentrations and increased LV fractional shortening and global peak systolic strain compared to controls not pre-treated with carvedilol [137].

This lack of benefit from the medical therapy could be due to the fact that the dominant clinical pattern is a progression from a dilated cardiomyopathy to a restrictive cardiomyopathy [138]. Restrictive cardiomyopathy predicts a reduced likelihood of success or benefit from pharmacotherapy used to treat other types of cardiomyopathies [139]. Given a lack of obvious efficacy and potential side effects such as hypotension and fatigue [136], teratogenicity [140], and increased risk of malignancy [141], the use of ACE-inhibitors in patients with chemotherapy-induced cardiomyopathy is controversial [136, 139].

Some patients with chemotherapy-induced cardiomyopathy progress to end-stage HF. Transplant is probably the last resort in patients with cardiomyopathy. A 2004 multi-institutional study concluded that heart transplants in patients with anthracycline-related cardiomyopathy can be successful, with 1-, 2-, and 5-year survival rates of 100%, 92%, and 60%, respectively [142]. More recently, the Pediatric Heart Transplant Study group concluded that long-term survival after heart transplantation for anthracycline-related cardiomyopathy was no different than that for matched patients with dilated cardiomyopathy [143].

10 Conclusion

Children and adolescents with childhood cancer are almost always treated with agents that have known cardiotoxic side effects. The survival of these patients has improved and as a result, we have a lot more survivors who experience cardiovascular complications. The effects of treatment-induced cardiomyopathy can occur at the time of treatment or months to years later. Given that chemotherapy-induced cardiac damage is often irreversible, it is important to find treatment strategies aimed at preventing or reducing the

cardiac injury. The effective implementation of these strategies must also be considered as many survivors fail to adhere to current screening guidelines [144]. The use of cardioprotective strategies, as well as the development of validated biomarkers identifying the risk of late cardiotoxic-related events and new drugs with fewer cardiotoxic effects, is vital to continue to improve both the short-term and long-term health of children with cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

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