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REVIEW

Chemotherapy-induced cardiotoxicity in children

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ABSTRACT

Introduction: With advances in clinical oncology, the burden of morbidity and mortality for cancer survivors due to the cardiac side effects of the chemotherapy is steadily increasing. Treatment-related cardiac damage is progressive and often irreversible. Primary prevention of cardiotoxicity during treatment is possible with strategies like limiting the cumulative anthracycline dose, the use of anthracycline structural analogs, and especially cardioprotective agents.

Areas covered: This review covers the various cardiotoxic chemotherapeutic agents, the pathophysiology of cardiotoxicity due to anthracyclines, and the clinical and subclinical presentations and progression of childhood anthracycline cardiotoxicity. We also discuss preventive measures and strategies, especially the cardioprotectant agent dexrazoxane where there is strong evidence-based support for its use with anthracycline chemotherapy. However, there is a paucity of evidence-based recommendations for diagnosing and treating cancer therapy-induced cardiovascular complications. Finally, we discuss the potential of cardio-oncology.

Expert opinion: There is no 'safe' anthracycline dose if the goal is normal long-term cardiovascular status but higher lifetime cumulative doses of anthracyclines, higher dose rates, female sex, longer follow-up, younger age at anthracycline treatment, pre-existing cardiovascular disease, and cardiac irradiation are associated with more severe cardiotoxicity. With deeper understanding of the mechanisms of the adverse cardiac effects and identification of driver mutations causing these effects, personalized cancer therapy to limit cardiotoxic effects can be achieved, such as with the cardioprotectant dexrazoxane.

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KEYWORDS
Childhood cancer; anthracycline; cardiotoxicity; survivorship; cardio-oncology

1. Introduction

The burden of childhood cancer is large. Recent estimates have revealed that >15,000 children are diagnosed with cancer every year in the United States [1]. With the advances in management over the years, there has been a rise in the rate of childhood cancer survivors from ~50% to ~80% from 1970 to 2010 [2,3]. As of 2005, nearly one-fourth of the almost 330,000 survivors of childhood cancer have survived longer than 30 years since diagnosis [4]. The focus of care for these survivors of childhood cancers has now shifted from not just the early survival, but also toward the long-term outcomes including chronic health conditions and health-related quality of life in adult survivors of childhood malignancies [5,6]. Unfortunately, the same treatments that cure cancer also increase the risk of adverse effects in other organ systems, especially the cardiovascular system [7].

The onset of these cardiotoxic effects is categorized as acute, or early or late chronic, depending on the time since anthracycline administration [8–10]. It was reported as early as the 1970s that patients receiving >500 mg/m^2 of the anthracyclines doxorubicin or daunorubicin experienced severe cardiotoxicity either during or shortly after treatment [11]. Moreover, it has been noted that anthracyclines result in cardiotoxicity (decreased left ventricular (LV) contractility and increased LV afterload) in a dose-related fashion [12,13]. Newer treatment protocols with limited chemotherapy dosing and accurate radiation targeting have reduced the acute symptomatic cardiovascular complications on frontline cancer treatment protocols significantly to less than 1% [13]. However, it is now clear that the cardiotoxicity of treatment is not limited to acute complications and that long-term survivors are at risk for progressive cardiovascular complications for the rest of their lives (Table 1) [12,14–18]. An in-depth understanding of the early and long-term sequela of antineoplastic drugs and their effects on the cardiovascular system is essential for not only the health-care professionals taking care of these patients but also, for the professionals from the pharmaceutical industry who will be instrumental in developing future drugs used for treatment.

2. Cardiotoxic therapies

Certain treatments of childhood cancer are cardiotoxic, especially anthracyclines and tyrosine kinase inhibitors (Table 2) [20]. Anthracyclines, such as doxorubicin, daunorubicin, and epirubicin, are among the chemotherapeutic agents commonly used to treat both hematologic

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Article highlights

- The number of survivors of childhood cancers has increased exponentially; survivors are at substantially increased long-term risk of morbidity and mortality from treatment-related cardiotoxicity
- There is no 'safe' dose of anthracycline but higher lifetime cumulative doses of anthracyclines, higher dose rates, younger age at treatment, longer follow-up after treatment, female sex, and cardiac irradiation are associated with more severe cardiotoxicity.
- There is a paucity of evidence-based recommendations for diagnosing and treating cancer therapy-induced cardiovascular complications.
- Treatment-related cardiac damage is progressive and often difficult to reverse.
- The key points in management of these toxicities are: mitigation by primary prevention and then effective management of the toxicity, which has already occurred, in order to minimize ongoing morbidity.
- With deeper understanding of the mechanisms of the adverse cardiac effects and identifications of driver mutations causing these effects, personalized cancer therapy to limit cardiotoxic effects may be achieved.

This box summarizes key points contained in the article.

therapy, however, is also a cardiotoxic cancer therapy and is often dose limiting when clinically significant cardiotoxicity develops [24,26]. Anthracyclines cause several adverse outcomes, which have been known and studied for decades. A study by Ewer et al. in doxorubicin-treated adult oncology patients showed a correlation between the cumulative doxorubicin dose and the grade of cardiotoxicity found on their endomyocardial biopsies by electron microscopy [27]. More than 50% of childhood cancer survivors have been treated with anthracyclines and show progressive cardiotoxicity [8]. The most important side effect of this class of medications is long-term cardiotoxicity, which has been well established [28], and is a major limitation of this class of medications [29,30]. The expression of heart failure (HF) in survivors treated with anthracyclines ranges from 1% to 16% according to some studies, but the true rate may be even greater with extended follow-up [16,31].

Table 1. Characteristics of 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 completing anthracycline therapy	>1 year after completing 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

Reproduced with permission from [8].

Table 2. Cardiotoxic effects of selected cytotoxic agents.

Treatment	Cardiotoxic effect
Anthracyclines: Daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone	Arrhythmias, pericarditis, myocarditis, HF, LV dysfunction
Liposomal anthracyclines: Pegylated liposomal doxorubicin hydrochloride (DOXIL®, CAELYX®)	HF, LV dysfunction, arrhythmias
Antimetabolites: Capecitabine, carmustine, clofarabine, cytarabine, 5-fluorouracil, methotrexate	Ischemia, chest pain, MI, HF, arrhythmias, pericardial effusions, pericarditis, hemodynamic abnormalities
Antimicrotubule agents: Paclitaxel, vinca alkaloids	Hypotension or hypertension, ischemia, angina, MI, bradycardia, arrhythmias, conduction abnormalities, HF
Alkylating agents: Busulfan, chlormethine, cisplatin, cyclophosphamide, ifosfamide, mitomycin	Endomyocardial fibrosis, pericarditis, tamponade, ischemia, MI, hypertension, myocarditis, HF, arrhythmias
Small-molecule tyrosine kinase inhibitors: Dasatinib, gefitinib, imatinib mesylate, lapatinib, erlotinib, sorafenib, sunitinib	HF, edema, pericardial effusion, pericarditis, hypertension, arrhythmias, prolonged QT interval, ischemia, chest pain
Monoclonal antibodies: Alemtuzumab, bevacizumab, cetuximab, rituximab, trastuzumab	Hemodynamic abnormalities, LV dysfunction, HF, thromboembolism, angioedema, arrhythmias
Interleukins: Denileukin, IL-2	Hypotension, capillary leak syndrome, arrhythmias, coronary artery thrombosis, ischemia, LV dysfunction
Miscellaneous agents: All-trans-retinoic acid, arsenic trioxide, asparaginase, etoposide, IFN-α, lenalidomide, 6-mercaptopurine, pentostatin, teniposide, thalidomide	Electrocardiographic changes, QT prolongation, torsades de pointes, other arrhythmias, ischemia, angina, MI, HF, edema, hypotension, bradycardia, thromboembolism, and retinoid acid syndrome that includes fever, hypotension, respiratory distress, weight gain, peripheral edema, pleural-pericardial effusions

HF: heart failure; LV: left ventricular; MI: myocardial infarction. Reproduced with permission from [19].

malignancies and solid tumors, and they have improved outcomes in patients with cancers such as acute lymphoblastic leukemia (ALL) and sarcomas [21–25]. Anthracycline

3. Pathophysiology of cardiotoxicity

As Andreas Moritz has written in his 2005 book entitled 'Cancer is Not a Disease – It's a Survival Mechanism': 'The

standard treatments for cancer are not meant to heal, but to destroy.' As a result, antineoplastic agents by design work most effectively on rapidly dividing malignant cells. But as a consequence they also damage normal body cells with high division rates thereby causing toxicity. Cardiomyocytes, unlike bone marrow and other cells, are often terminally differentiated cells that have a limited capacity to regenerate; hence, they are particularly vulnerable to long-term damage from these medications. Also, children are different from adults in drug utilization rates and their subsequent effects. Children have differences in drug metabolism (drug absorption, metabolism, and excretion) and drug effects are more likely to have long-term consequences following drug administration. With continuously improving medical management, most survivors of childhood cancer live for at least a decade after successful treatment of their cancer [32]. The small, subclinical changes due to the side effects of toxic chemotherapeutic medications become more severe over a long period of time and cause marked disability for childhood cancer survivors that may often not be experienced by their adult malignancy survivor counterparts.

A recent study showed that the mitochondria from adults are 'apoptosis refractory' [33]. In contrast, the mitochondria from the heart and brain tissues in young mice and humans are primed for apoptosis, predisposing them to undergo cell death in response to genotoxic damage. This supports the hypothesis that young pediatric cancer patients may be more predisposed to the severe side effects of toxic chemotherapy than adult cancer patients in whom this apoptotic machinery is almost absent [33].

Various antineoplastic medications like cyclophosphamide, cytosine arabinoside, cisplatin, ifosfamide, paclitaxel, 5-fluorouracil, and amsacrine have been known to cause cardiomyocyte damage. These groups of antineoplastic medications express their effects in several ways including: (A) by their inhibition of topoisomerase II activity thereby preventing uncoiling of DNA and (B) by their intercalation into base pairs of DNA. By doing this they, in turn, inhibit replication and transcription of neoplastic cells [20,34].

The mechanism of anthracycline-induced cardiotoxicity is complex but one of the acknowledged mechanisms is the 'oxidative stress hypothesis' (Figure 1) [36–39]. Cardiolipins, found abundantly on the inner cell membrane of mitochondria have an increased affinity for anthracyclines allowing for their increased entry [40,41]. Anthracyclines enter cells by passive diffusion and can reach intracellular concentrations much higher than in the extracellular compartments. By forming complexes with iron intracellularly, anthracyclines lead to the production of free radicals and reactive oxygen species, which lead to cellular damage and death. They also cause cell membrane damage by lipid peroxidation. Cardiomyocytes have an abundance of mitochondria. Moreover, anthracyclines cause depletion of glutathione peroxidase (antioxidant) thus explaining the vulnerability of cardiomyocytes to anthracycline-induced damage [42,43]. Several other

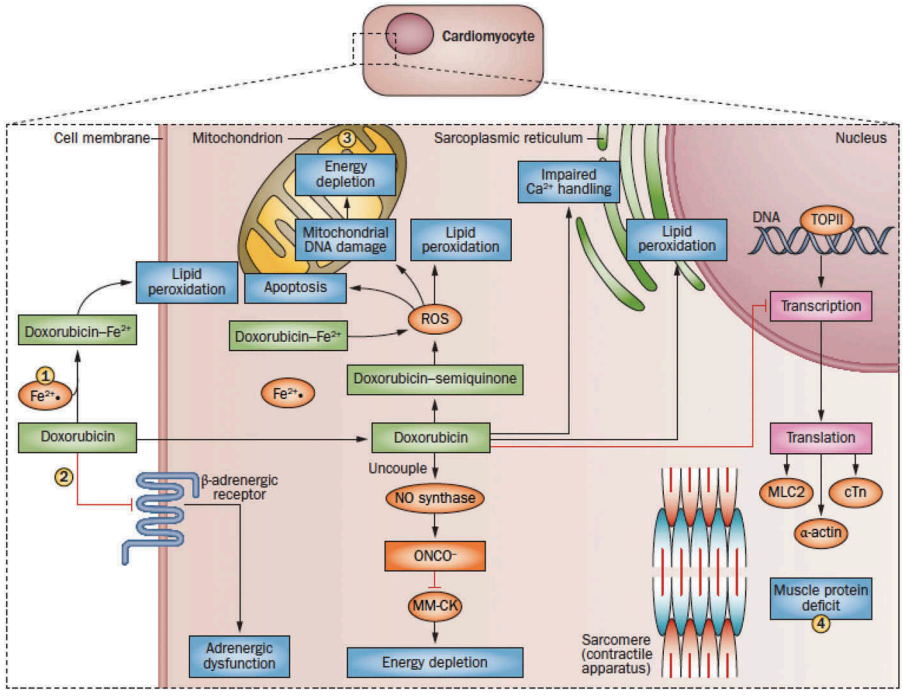

Figure 1. **Potential opportunities for cardioprotection. Doxorubicin chemotherapy has a range of effects on cardiomyocytes**. It induces lipid peroxidation at the cell and mitochondrial membranes by way of complexing with Fe^{2+} and induces apoptosis, mitochondrial DNA damage and energy depletion through its production of ROS. Furthermore, it impairs Ca^{2+} processing in the sarcoplasmic reticulum and inhibits the transcription of important muscle elements, weakening the heart muscle. It also down-regulates adrenergic receptors and interrupts cell signaling. (1) Administration of dexrazoxane can prevent Fe^{2+} complex formation. (2) Intravenous immunoglobulin therapy can reduce inflammatory cytokines. (3) L-carnitine can bolster mitochondrial function. (4) Anti-HF therapies, such as angiotensin-converting-enzyme inhibitors and β-blockers, can prevent further damage. Abbreviations: cTn, cardiac troponin; MLC2, myosin light chain 2; MM-CK, myofibrillar isoform of the CK enzyme; ROS, reactive oxygen species; TOPII, topoisomerase 2. [Reproduced with permission from Nature Publishing Group [35].

mechanisms of cardiotoxicity include the upregulation of nitric oxide synthetase and the alteration of gene expression, causing impaired creatine kinase activity and function in mitochondria [44,45]. By impairing mitochondrial calcium regulation, they also cause instability of the mitochondrial membrane, decrease ATP synthesis, and ultimately may cause cell death. Many of these subcellular sequelae progress for weeks after exposure to anthracyclines providing insight into mechanisms of chronic cardiomyopathy [46].

Topoisomerase-II β (Top2β) alterations have also been documented as a mechanism of doxorubicin-mediated cardiotoxicity [47,48]. Top2β is an upstream target for anthracyclines. It is found in terminally differentiated cardiomyocytes. An animal study [49] comparing dexrazoxane and inorganic nitrates to prevent anthracycline cardiotoxicity revealed that while inorganic nitrates were ineffective, dexrazoxane prevented all investigated molecular, cellular, and functional perturbations that were induced by daunorubicin. In that study, dexrazoxane consistently and significantly depleted the Top2β protein in both primary neonatal cardiomyocytes and H9c2 cells as well as in rabbit hearts. Studies by Ichikawa et al. [50], and Zhang et al. [47], suggest that targeting both mitochondrial iron and topoisomerases is protective against the cardiotoxicity of doxorubicin. A study by Martin et al. [51] demonstrated that topoisomerase II-inactive 3-carbon linker bisdioxopiperazine, an analog of dexrazoxane, does chelate iron and protect against doxorubicin-induced LDH release from primary rat cardiomyocytes *in vitro*. This supports the theory of Top2β modulation by dexrazoxane as a mechanism behind its cardioprotection. In a recent study, the peripheral blood leukocytes' Top2β expression was higher in anthracycline-sensitive patients (patients who demonstrated a decrease LV ejection fraction (LVEF) ≥ 10% from baseline and who also showed an LVEF < 50%, despite receiving a cumulative doxorubicin dose of ≤250 mg/m^2) than in anthracycline-resistant patients (who received a cumulative doxorubicin dosee of ≥450 mg/m^2 and who maintained an LVEF ≥ 50%) [52]. In a mouse model, deleting cardiomyocyte Top2β prevented anthracycline-induced cardiotoxicity [53]. This provides new strategies for preventing anthracycline-induced cardiotoxicity and possible uses of Top2β as a surrogate marker for assessing the susceptibility to anthracycline-induced cardiotoxicity.

The susceptibility of cardiomyocytes to anthracyclines is manifold and not hinged on a single theory. Cardiomyocytes have a limited regenerative potential and hence once damaged by chemotherapeutic agents, they may never recover.

In addition to myocardial structural damage, antineoplastic therapies may also affect the conduction tissue within the heart that may lead to bradycardia (paclitaxel and thalidomide); arrhythmias and QT interval prolongation (amsacrine and anthracyclines); myocardial ischemia via coronary vasospasm (antimetabolites and 5-fluorouracil); LV dysfunction/HF (anthracyclines, tyrosine kinase inhibitors, alkylating agents, and cisplatin) (Table 3).

Table 3. Examples of pediatric chemotherapeutics agents associated with cardiotoxicity.

Adverse effect	Class/compound	Pathogenesis
Bradycardia	Taxanes/paclitaxel	Hypersensitivity
Arrhythmias/QT prolongation	Amsacrine	Interference with HERG currents
	Anthracyclines (doxorubicin)	Inhibition of cardiac kinases
	Sunitinib	
	Anthracyclines (doxorubicin)	Interference of ion channels
Myocardial ischemia	Antimetabolites/5-fluorouracil	Coronary vasospasm
Left ventricular dysfunction/HF	Anthracyclines (doxorubicin), Cisplatin	Oxidative Coronary artery fibrosis

HF: heart failure; HERG: human ether-a-go-go related.
Reproduced with permission from the American Heart Association [54].

4. Progression of cardiotoxicity

Anthracycline cardiotoxicity can be categorized at the time of presentation as either acute or chronic, with chronic toxicity further categorized as early- or late-onset (Table 1) [55]. Acute symptomatic cardiotoxicity presents in less than 1% of pediatric patients being treated on frontline cancer protocols. It may present within a few hours of infusion or during the course of the treatment [8,13,55], and often manifests as arrhythmias and electrocardiographic abnormalities. Sometimes, at very high doses, it can present as HF or as a myocarditis-pericarditis syndrome [8,13,55,56]. It generally resolves on discontinuation of the treatment [8,56]. In a follow-up study of survivors treated with anthracyclines and with acute HF, all recovered temporarily, although nearly half later had recurrent HF [12].

Early onset cardiomyopathy may show LV dysfunction, electrocardiographic changes, or clinical HF [8,9,13,29,55,57]. According to our 2005 study, these anthracycline-treated pediatric ALL patients initially developed a dilated cardiomyopathy with reduced LV fractional shortening (LVFS) and LV contractility along with LV dilation. Slowly, with time, it changed to a pattern found in patients with a restrictive cardiomyopathy with normal to reduced LV dimensions along with significantly reduced LV wall thickness, LVFS, and LV contractility [58]. In 115 survivors of ALL or osteosarcoma treated with the doxorubicin, 6 years after treatment, LV wall thickness was decreased relative to body-surface area which impaired LV systolic function, limited LV contractility, and reduced cardiac output [12,15,16]. At 8 years after treatment, we found that younger age at diagnosis and an increased follow-up time were associated with decreased LV wall thickness for body-surface area and female sex. We also observed that an increased cumulative anthracycline dose was associated with reduced LV contractility, indicating unhealthy heart muscle (Figure 2) [15]. At the 12-year follow-up mark, we found that LV mass for body-surface area, as well as LV contractility, progressively declined, indicating that the health and growth of cardiac muscle cells in the LV worsened (Figure 3) [16]. This study also reported that even survivors who received low cumulative doses of anthracyclines were still at risk for chronic cardiotoxicity years after therapy, indicating that there is no safe dose of anthracyclines that leaves a long-term survivor completely free of associated cardiovascular abnormalities. At a mean of 17.3-years follow-up, these 115 survivors had a mean LV dimension

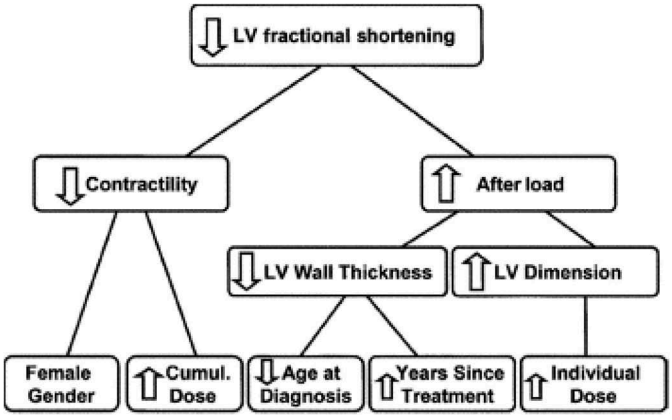

Figure 2. **Factors associated with cardiac abnormalities and progression to left ventricular dysfunction in childhood cancer survivors who received anthracyclines**. [Reproduced by permission [59].

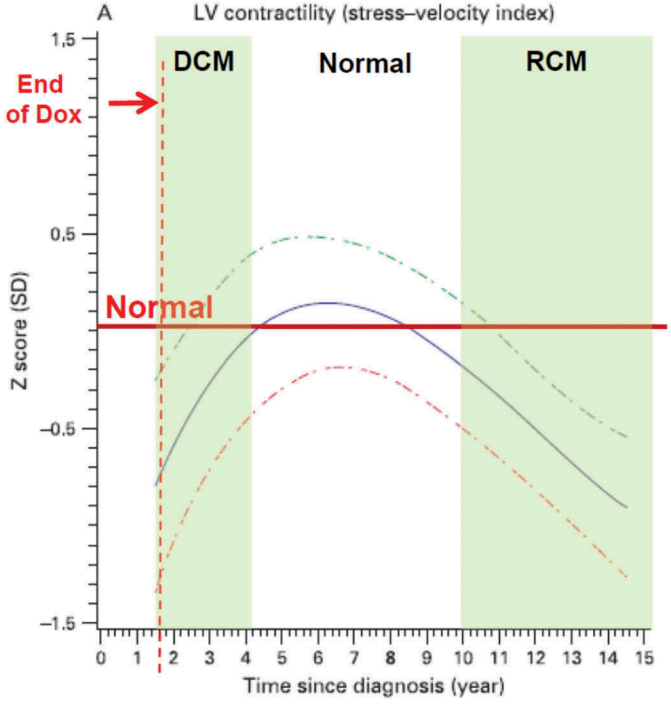

Figure 3. **Changes in left ventricular structure and function over time, reported as Z-scores, from a study of 115 survivors of childhood acute lymphoblastic leukemia**. The solid line is the overall group mean, and dashed lines are the upper and lower bounds for the 95^{t}% confidence interval for left ventricular contractility (LV stress-velocity index). Dox, doxorubicin; CDM, dilated cardiomyopathy; RCM, restrictive cardiomyopathy [Reproduced with permission from [16].

z-score adjusted for body-surface area that decreased and the LV posterior wall thickness *z*-score adjusted for body-surface area subsequently increased, resulting in an abnormally reduced LV thickness-to-dimension ratio, indicating pathologic LV remodeling (Figure 4). This shrinking myocardial cavity for body-surface area (which we have called 'Grinch Syndrome'), indicating a heart too small for body size, is a chronic cardiomyopathy, which may result in HF, heart transplantation, or premature death in long-term survivors [61]. Abnormal LV structure and function, as well as a restrictive-like cardiomyopathy pattern, are also found in other long-term follow-up studies of other anthracycline-treated survivors [62–64]. Endomyocardial biopsies from survivors with chronic anthracycline cardiotoxicity display both individual cardiomyocyte hypertrophy and cytoplasmic and nuclear enlargement [12,14]. There is evidence of late deterioration and death >10 years after anthracycline therapy due to the replacement of degenerated cardiomyocytes by fibrosis. Early acute toxicity presents with vacuolization and long-standing damage presents with fibrosis. However, hemorrhage and edema have also been reported in the biopsy. Endomyocardial biopsy has the advantage of identifying the etiology of deterioration (e.g. infectious myocarditis or monitoring the degree of anthracycline damage) [65]. The LV faces the increasing afterload of the systemic circulation and hence is likely more susceptible to or likely to demonstrate anthracycline damage leading to systolic and diastolic dysfunction than the right ventricle (RV). A study in rabbits evaluated how the RV and the LV were affected in rabbits exposed to daunorubicin [66]. They found that the RV was less affected than the LV. Daunorubicin altered various sarcomeric proteins in the LV, affected calcium regulation in the LV cardiomyocytes, and caused extensive remodeling of the extracellular matrix in the LV with lesser changes found in the RV. The RV however is also affected. Historically, RV mechanics were more difficult to assess with 2D echocardiographic imaging. Newer studies have found that the RV is also affected by anthracycline cardiotoxicity [67–69]. Treatment-related damage likely results in both cardiac cell death and permanent injury to many of the remaining cardiac cells, especially stem cell populations.

5. Cardiac monitoring

Given the increased prevalence of cardiotoxicity and cardiovascular complications in anthracycline-treated childhood cancer survivors, it is prudent to assess cardiac structure and function on a periodic basis. Methods of assessing cardiac function (echocardiography, cardiac MRI, and radionuclide ventriculography) often detect abnormalities only after a certain degree of cardiomyocyte damage has occurred. Hence, detecting myocardial injury before irreversible damage has occurred can be challenging. The guidelines published by Steinherz et al. [70] in the 1990s for monitoring children during chemotherapy (utilizing LVFS and LVEF, radionuclide angiography and endomyocardial biopsy) were questioned by Lipshultz et al. as no evidence was provided that such screening predicted early or late cardiac adverse events, or improved overall quality of life for a patient and their family over a lifespan [71]. For long-term monitoring, the Children's Oncology Group guidelines recommend life-long echocardiographic screening every 3–5 years in survivors treated with anthracyclines or cardiac radiation [72,73], which have been further refined [74,75]. Although these guidelines may reduce risk for HF in survivors, they are still not evidence based [74].

Echocardiography is a commonly used modality for monitoring childhood cancer survivors. Modifying chemotherapeutic dosage during oncologic therapy based on changes in echocardiographic measurements in anthracycline-treated childhood cancer patients without symptomatic cardiovascular disease should require evidence that withholding potentially lifesaving chemotherapy will improve overall survival and quality of life.

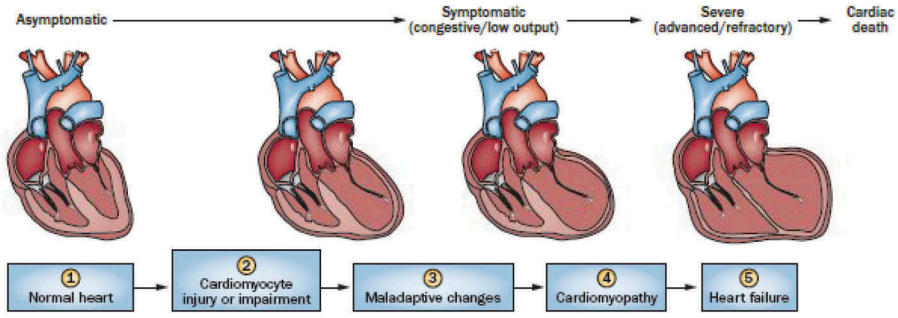

Figure 4. **Stages in the development of pediatric ventricular dysfunction**. Stages in the course of pediatric ventricular dysfunction. (1) Primary prevention is possible at this stage by reducing risk factors in high-risk populations (such as those receiving anticancer therapy). (2) Secondary prevention is possible at this stage to reduce the effects of the treatment-induced injury. (3) Secondary prevention is also possible at this stage. (4) Clinically significant conduction and rhythm abnormalities might be observed. (5) Radical therapies might be required at this stage (such as heart transplant) if there is failure of medical management. Preventive strategies are progressively less effective as the toxicity increases. Treatment strategies have a greater impact when used to treat the more-diseased heart, but have longer effects if initiated early. Biomarkers and surrogate end points are potentially useful at early stages to alter the course with interventions, and are potentially useful at later stages to aid decisions about transplantation [Reproduced with permission from Nature Publishing Group [60].

With the current monitoring protocols the probability of HF is low and hence utilizing traditional measures of evaluating cardiac function (LVEF) as a monitoring tool has an unacceptably low predictive value. Moreover, withholding chemotherapy in an asymptomatic individual because of changes in LVEF is more likely to cause oncologic treatment failure than decreasing the likelihood of irreversible cardiac injury [76]. Other echocardiography techniques are being utilized to evaluate LV systolic dysfunction (LV stress velocity index), LV diastolic function, global ventricular function (myocardial performance index), and LV mechanics (2-dimensional strain and strain rate) [77–81], but they may have limited specificity to detect cardiomyocyte injury [76]. More formal studies are needed to assess the impact of such monitoring for long-term management.

Cardiac MRI may be beneficial to assess myocardial function, ventricular mass, and subendocardial damage more accurately, particularly when acoustic windows are limited. Although MRI was able to detect acute as well as chronic subclinical signs of cardiac involvement [82], how it correlates with subsequent clinically significant endpoints is yet to be evaluated. Cardiac MRI is also time consuming, has limited availability, and is costly, thus, limiting the utility of this modality.

More recently, serum biomarkers of cardiotoxicity (cTnT, cardiac troponin I [cTnI] and N-terminal pro-brain natriuretic peptide [NT-proBNP]) are increasingly being used to monitor childhood cancer patients for cardiotoxicity. Serum cTnT and NT-proBNP have been validated as serum biomarkers for predicting during anthracycline therapy which patients may subsequently experience years later cardiotoxicity as long-term cancer survivors [18]. Lipshultz et al. evaluated the use of cardiac biomarkers during anthracycline treatment in childhood cancer patients [83]. We randomized 205 patients with high-risk ALL to receive doxorubicin or doxorubicin with the cardioprotectant dexrazoxane. Serum cTnT levels and NT-proBNP levels were detectable or elevated for some children during the first 90 days of therapy. Measureable serum cTnT levels were significantly associated with lower LV mass *Z*-scores and LV end-diastolic posterior wall thickness *Z*-scores. They were also marginally associated with a reduced LV thickness-to-dimension ratio 4 years later (Figure 5). Also, higher serum NT-proBNP levels were associated with an abnormally reduced LV thickness-to-

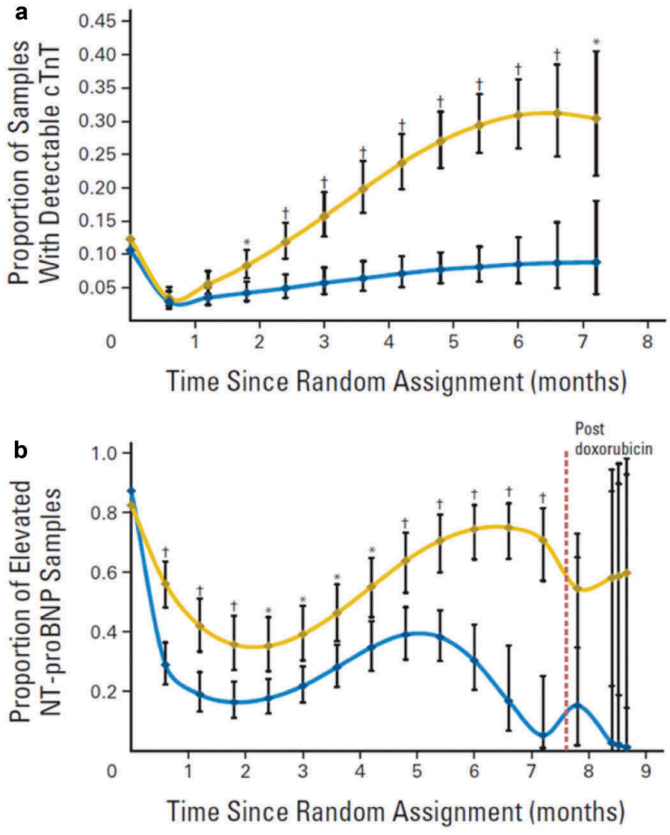

Figure 5. **Model-based estimated probability of having** (a) **an increased cardiac troponin T (cTnT) concentration or** (b) **an elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration in patients treated with doxorubicin, with or without dexrazoxane**. The doxorubicin-dexrazoxane group is indicated by the blue line, the doxorubicin group by the gold line. Vertical bars show 95% confidence intervals. Increased cTnT is defined as a value >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 ≥150 pg/mL for children <1 year old and ≥100 pg/mL for children aged ≥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 ($P = 0.24$). [Permission from American Society of Clinical Oncology © Lipshultz SE, et al. 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. Reproduced with permission from [83].

Table 4. Risk factors for anthracycline-related cardiotoxicity.

Risk factor	Notes	References
Cumulative anthracycline dose	Cumulative doses >500 mg/m^2 associated with significantly elevated long-term risk	[12,13,15,16]
Length of post-therapy interval	Incidence of clinically relevant cardiotoxicity increases progressively post-therapy	[12,15,16]
Rate of anthracycline administration	Prolonged administration to minimize circulating dose volume may decrease toxicity; results are mixed	[85]
Individual anthracycline dose	Higher individual anthracycline doses are associated with increased late cardiotoxicity, even when cumulative doses are limited	[15,16]
Type of anthracycline	Liposomal encapsulated preparations may reduce cardiotoxicity. Results for anthracycline analogs and cardiotoxicity differences are conflicting	[29,59,86]
Radiation therapy	Cumulative radiation dose >30 Gy; before or concomitant anthracycline treatment	[9,55]
Concomitant therapy	Trastuzumab, cyclophosphamide, bleomycin, vincristine, amsacrine, mitoxantrone may increase susceptibility/toxicity. Others agents have also been implicated	[28,55]
Preexisting cardiac risk factors	Hypertension; ischemic, myocardial, and valvular heart disease; prior cardiotoxic treatment	[28]
Comorbidities	Diabetes, obesity, renal dysfunction, pulmonary disease, sepsis, infection, endocrinopathies, electrolyte and metabolic abnormalities, and pregnancy	[28]
Age	Both young and advanced age at treatment are associated with elevated risk	[12,15]
Sex	Females are at greater risk than males	[15]
Additional factors	Trisomy 21; African American ancestry	[13]

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dimension ratio, suggesting pathologic LV remodeling by echocardiography performed 4 years later. In addition, before, during, and after treatment, a higher percentage of children had increased levels of NT-proBNP (indicating increased myocardial stress) than had abnormal cTnT levels (indicating cardiomyocyte injury or death), suggesting that NT-proBNP may detect cardiac stress before irreversible cardiomyocyte damage or cell death [83]. Another study by Lipshultz et al. studied the cardiovascular status of 156 childhood cancer survivors exposed and 45 unexposed to cardiotoxic therapy compared with 76 sibling controls [18]. One of the important findings of this study was that both exposed and unexposed survivors, compared to siblings, had higher serum NT-proBNP levels (81.7 and 69.0 pg/ml, respectively, vs. 39.4 pg/ml) suggesting increased myocardial stress in both groups. In this study, we also showed that both exposed and unexposed survivors had a higher age-adjusted, predicted-to-ideal 30-year risk of myocardial infarction, stroke, or coronary death [18]. This suggests that even childhood cancer survivors not receiving cardiotoxic treatments have cardiovascular abnormalities. Further research is needed in this area to evaluate the utility of cardiac biomarkers in tailoring cancer chemotherapy and improving long-term outcomes in these patients.

The optimal timing and frequency of cardiovascular monitoring in cancer survivors remains controversial as the available guidelines are not consistent in their recommendations and are based on limited evidence. A comprehensive AHA scientific statement summarizing a large amount of evidence in the field of cardiotoxicity after treatment of cancer in children, adolescents, and young adults was published by Lipshultz et al. which may be valuable to clinicians in providing available evidence related to the clinical care and monitoring of these patients [54].

6. Risk factors

There are several risk factors that contribute to late-onset anthracycline-induced cardiotoxicity, including younger age at treatment, increasing time since treatment, female sex, higher cumulative doses, higher dose rates, elevations of serum cTnT or NT-proBNP measurements before or during anthracycline therapy, and HF during anthracycline therapy [84] (Table 4).

A comprehensive study by Lipshultz et al. [15] reviewing 120 children and adults treated with anthracyclines for ALL and osteosarcoma revealed that female sex was an independent risk factor cardiac abnormalities along with a higher dose rate of doxorubicin administration. This has been confirmed in other pediatric studies [87,88]. Anthracycline-induced cardiomyopathy may be acute or subacute, occurring within 1 year of treatment, or late, occurring several years post administration [55,57]. As mentioned, dilated cardiomyopathy may be observed immediately after high-dose anthracycline treatment. However, a restrictive cardiomyopathy (LV diastolic dysfunction) develops in many survivors over time, placing them at risk for HF with preserved LV systolic function [84].

Many long-term follow-up studies have documented the cardiac effects of anthracyclines. For example, among 755 patients with localized osteosarcoma treated with doxorubicin (median age, 15 years; range, 3–40 years) the incidence of HF (New York Heart Association Functional Heart Failure Classification System's moderate to severe HF classes II–IV) was 1.7% (13/755) at a median follow-up of 8.5 years. Of these 13 patients, 6 died and 3 needed a heart transplant [23]. The incidence was higher in females and in those treated with a higher cumulative anthracycline dose. Another retrospective longitudinal study of children less than 17 years old with Ewing sarcoma found a high incidence of cardiotoxicity as detected by echocardiography [89]. Of the 71 patients, LV function, as assessed by LVEF, declined in 17 after completing therapy. The strong association between the cumulative anthracycline dose and cardiotoxicity appears to become more important with time from treatment, as shown in a study of nearly 5000 survivors treated with anthracyclines who described their cardiac health at up to 30 years after treatment [90]. A longitudinal study of 22 survivors with

malignant bone tumors treated with anthracyclines found that adverse cardiac structural changes resulted in marked and progressive cardiac dysfunction [91]. The risk of HF, valvar disease, and pericardial disease in survivors is five times as high as that of healthy siblings, and cardiac dysfunction will develop in up to half of survivors within 20 years after anthracycline treatment [90]. Despite the vast amount of data documenting the adverse cardiac effects of doxorubicin and other anthracyclines, these drugs have remained critical components of therapy for many years, particularly for patients with hematologic malignancies and solid tumors.

Because cardiac abnormalities do not develop in all children exposed to anthracyclines, and because the clinical severity of such abnormalities varies greatly, determining the factors that may increase their likelihood is greatly important. As stated, higher cumulative doses of anthracyclines, higher anthracycline dose rates, the use of concomitant cardiotoxic therapies (such as mediastinal radiation), younger age at treatment, increasing time since treatment, female sex, preexisting cardiovascular disease including elevations in serum cTnT or NT-proBNP concentrations measured before and during anthracycline therapy, and HF during anthracycline therapy, are risk factors for anthracycline cardiotoxicity [62,84].

Genetic factors can identify individuals at higher risk of anthracycline cardiotoxicity and so may be useful in preventing cardiotoxicity [92]. This hypothesis is supported by the greater cardiac susceptibility of patients with trisomy 21 and black race [13,92,93]. Genetic variations and polymorphism of the NAD(P)H oxidase and doxorubicin efflux transporters have been shown to modulate and contribute to acute and chronic cardiotoxicity associated with anthracycline [94].

Krajinovic et al. confirmed clinically relevant associations between *NOS3* and *ABCC5* gene variants and their contribution to chronic cardiotoxicity following doxorubicin treatment [95]. Patients with an A-1629 T genotype variant in the ABCC5 gene showed significantly more impaired LV function with decreases in LVEF and shortening fractions. Another genotype variant of the NOS3 gene, G-894 T, demonstrated a more protective effect by showing a relative increase in the LVEF.

Given the importance of iron, and its potential genetic involvement in anthracycline-induced cardiac injury, Lipshultz et al. studied mutations of the hemochromatosis gene (HFE), which is associated with hereditary hemochromatosis [96]. We found that in 184 survivors of childhood ALL, 10% carried a mutation in the HFE C282Y allele. Heterozygosity for C282Y was associated with multiple elevations in cTnT concentrations, indicating myocardial injury, after doxorubicin therapy, when controlling for dexrazoxane treatment. The presence of the C282Y mutation resulted in nearly a ninefold increased risk of myocardial injury when these children with ALL were treated with doxorubicin when compared to similar children without the C282Y allele. We also found that patients with the C282Y and/or H63D allelic variants had significantly lower LV function, LV mass, and wall thickness 2 years after diagnosis, when compared to the normal population [96].

These studies, along with others [97], have shown that a genetic predisposition exists for anthracycline-induced cardiotoxicity. Genetic screening for these mutations may help guide us in the future toward developing individual treatments for susceptible patients and thus, limit the long-term incidence of cardiotoxicity.

Despite these population-based risk factors, determining the individual risk for a specific patient is still limited. Thus, at present, all children who receive anthracycline therapy should be followed closely during and after treatment for cardiotoxicity, including long-term follow-up into adulthood. The above risk factors are currently used to guide the frequency of follow-up exams and may also help increase our understanding of the underlying pathophysiologic mechanisms.

7. Treatment of anthracycline-induced cardiotoxicity

Treating and curing cancer, in most cases, involves a multimodality approach. Children and adolescents with cancer are at significant risk of cardiotoxicity and several additional adverse effects that often have delayed onset from surgical resection, chemotherapy, radiation, and newer biologic and targeted therapies. Common drugs used in treating anthracycline-induced cardiotoxicity are angiotensin-converting enzyme inhibitors (ACEI), beta-blockers, and growth hormone replacement therapy. However, despite these options, there has been no established standard-of-care therapy for chemotherapy-induced cardiac disease. Beta-blockers and ACEI are standard-of-care medications for treating and managing HF, but their effects on progression-free or overall survival have not been established [54]. The benefial effect of enalapril, an ACEI, in children or adolescents with cancer who developed either asymptomatic LV dysfunction or HF delayed but did not prevent progression of disease [85,98]. The goal of therapy is to prevent or slow LV remodeling rather than to treat the cause of cardiomyopathy [99]. This emphasizes the need for new and specific strategies to treat anthracycline-related cardiotoxicity and that methods of preventing these complications would be of great clinical utility.

ACEI were hypothesized to reduce LV afterload to compensate for decreased LV wall thickness and to ease progression of HF. However, ACEI did not provide a sustained benefit in treating survivors with anthracycline-related cardiotoxicity, raising concerns that the risks of these drugs may outweigh their benefit in this population [85,98]. In our study that examined 18 survivors who had received enalapril after treatment with doxorubicin at Boston Children's Hospital from 1984 to 1989, 6 of whom were in HF at the beginning of therapy, during the first few years of enalapril therapy, mean LV afterload and diastolic blood pressure were significantly reduced [85]. Mean LVFS also improved, although LV wall thickness did not. After 6–10 years on enalapril, these improvements were no longer evident. Mean LV wall thickness for body-surface area steadily declined. All 6 patients in HF when enalapril therapy began had died or undergone heart transplant, and 7 of the 12 originally asymptomatic patients had progressed to HF. This study indicates that, although ACEI may have had some short-term benefit, they did not prevent the progression of disease nor have sustained effects.

In this survivor population, enalapril-induced improvement in LV structure and function was transient. Enalapril did not prevent, but merely delayed, progression, for a 6- to 10-year

benefit for patients with asymptomatic LV dysfunction before returning to baseline. For enalapril-treated HF patients on this study there was only a 2- to 6-year benefit. All HF patients progressed to cardiac transplantation or cardiac death within 2–6 years [85,98]. Enalapril did not prevent progressive LV wall thinning for body-surface area, the primary defect that results in increased LV afterload and decreased LVFS. Limiting hypertrophic growth in a developing child may have detrimental consequences over a lifespan related to the long-term exacerbation of inadequate hypertrophy for body-surface area related to doxorubicin and then to enalapril. Enalapril did not address the primary defect of an inappropriately thin LV wall for body-surface area. Enalapril reduced LV afterload by a short-term lowering of diastolic blood pressure and LV dilation [85,98].

The 'AAA' (ACEI After Anthracycline) randomized, double-blind, placebo-controlled trial of enalapril of 146 childhood cancer survivors showed that the only significant cardiac finding was that there was a fall in LV end-systolic stress in the first year of enalapril therapy based on a fall in blood pressure due to ACEI ($P = .036$) [100].

It is important to understand the differences between anthracycline cardiomyopathy (ACM) and dilated cardiomyopathy (DCM). ACM differs from ischemic, postinfectious, and idiopathic DCM. In both the AAA study [100] and our study [54] there was a notable absence of ventricular remodeling in response to the fall in LV wall stress. In most DCM patients, ACEIs induce reverse ventricular remodeling with a reduction in ventricular volume and an improved mass-to-volume ratio, which further reduces wall stress and improves cardiac function. In both studies, despite a marked fall in wall stress, ventricular size and thickness did not change. In contrast to other forms of DCM, the natural history of ACM is characterized by minimal, nonprogressive dilation. The natural history of ACM and the response to ACEI therapy is unlike that of DCM, but is more characteristic of a restrictive cardiomyopathy, a disease class that does not benefit from ACEI therapy. Further, many AAA study participants also received cardiac irradiation, a therapy also associated with the development of a late restrictive cardiomyopathy.

It is important to note that the available data does not address whether the risk of ACEI therapy in patients with ACM exceeds those in other forms of DCM. Therefore, the wisdom of recommending ACEI use based on the applicability of trials conducted in other patient groups should be questioned. The clinical pattern of a dominantly restrictive cardiomyopathy predicts a reduced likelihood of benefit. Current data are also inadequate to address the risk associated with ACEI therapy of asymptomatic LV dysfunction in this population. Any adverse effects of long-term therapy clearly increase the risks for these patients, purely on the basis of markedly longer exposure. Further, these patients may be at increased risk for potential adverse events. Therefore, these findings argue against the routine use of ACEI therapy in patients with asymptomatic LV dysfunction secondary to ACM.

There are a few theoretical ACEI concerns in this population, using enalapril as an example. The first is that an excess rate of gastrointestinal cancers relative to placebo has been observed in several large trials of non-oncology adult patients receiving pronged ACEI therapy [85,98]. This may be more of a concern to younger cancer survivors already at increased risk for relapsed primary or secondary malignancies. Second, survivors are at increased global risk for premature atherosclerotic heart disease, a risk that may also be affected by ACEI therapy. As well, the unknown effects of chronic neurohormonal suppression or other side effects of long-term enalapril therapy in this population are a concern. Dizziness, hypotension, and fatigue were common problems for enalapril-treated AAA participants [85,98]. The considerable cost of an unproven potentially life-long therapy in a young patient population with large past medical expenses and lifetime insurance limits is a risk in ACEI therapy. As well, there are compliance issues for daily potentially lifelong ACEI use for asymptomatic patients. The effects do not appear to last forever raising other concerns. Understanding of other potentially adverse drug interactions with this therapy for this population is unknown. For females of childbearing age, ACEI use may cause fetal kidney abnormalities if taken during pregnancy. Finally, the potential for healthy, asymptomatic survivors to feel or be treated differently from their peers for taking chronic medications, may increase the likelihood of these children feeling like 'cardiac cripples.' [85,98]

The efficacy of ACEI therapy in anthracycline-treated, long-term survivors of childhood cancer remains an unanswered, but is an important question. No study has shown any beneficial effects of ACEI in childhood survivors on improving quality of life, long-term benefit, or reducing progression to HF or death. The potential adverse effects of this therapy in patients with ACM argue against using this therapy, especially without convincing evidence of efficacy [85,98].

Beta-blockers, which are beta-adrenergic receptor antagonists, block sympathetic stimulation to the heart, among other effects, and reduce cardiac demand, which is hypothesized to slow the progression of anthracycline-related cardiotoxicity [29]. Carvedilol is a frequently used beta-blocker as it simultaneously reduces cardiac demand as a nonselective beta-blocker and reduces LV afterload as an alpha-1-blocker through systemic vasodilation. In a randomized trial of 50 children with newly diagnosed ALL treated with doxorubicin, with or without carvedilol pretreatment, treatment reduced LV systolic function and increased plasma troponin I and lactate dehydrogenase concentrations. Pretreatment with carvedilol significantly increased LV systolic function and inhibited doxorubicin-induced increases in plasma troponin I and lactate dehydrogenase concentrations. However, the follow-up was short, so a sustained effect must still be examined [101]. A more recent randomized controlled placebo-based trial in 91 women with breast cancer showed that the prophylactic use of carvedilol inhibited anthracycline-induced cardiotoxicity [102].

8. Preventing cardiotoxicity

In addition to monitoring and treating cardiotoxicity among survivors, preventing cardiotoxicity is now a priority. Preventive medications given concurrently with chemotherapy regimens, such as dexrazoxane and liposomal formulations of doxorubicin, can reduce anthracycline-induced

cardiotoxicity, as can addressing the life-style risk factors for anthracycline-induced cardiotoxicity [18]. The potential for developing new and improved mechanisms to treat individual patients based on their specific genetic traits and risk factors should be considered when possible [95,96]. Cardioprotective medications have been a primary focus for preventing anthracycline-induced cardiotoxicity.

Dexrazoxane, first studied in beagles in the early 1980s [103], prevents cardiotoxicity among women with advanced breast cancer and has been approved by the US Food and Drug Administration for this indication [104–107]. Dexrazoxane is believed to act in part by chelating iron and ultimately interfering with iron-mediated free radicals (Figure 1) [35,54,60,108]. Lyu et al. showed that dexrazoxane shifts Top2's configuration to a close-clamp form by tight binding to Top2's ATP-binding sites, preventing anthracyclines from binding to the Top2 complex [109,110].

Since these initial studies in adults, several studies have been conducted in children and adolescents with cancer treated with anthracyclines. In an open-label, randomized trial of children and adolescents with sarcomas treated with doxorubicin-containing chemotherapy, with or without dexrazoxane, those receiving dexrazoxane had less subclinical cardiotoxicity, smaller decreases in LVEF, and received higher cumulative doses of doxorubicin with no difference in event-free or overall survival rates [22]. The Dana-Farber Cancer Institute's Childhood ALL Consortium Protocol 95–01 determined that dexrazoxane was associated with decreased myocardial injury among children with ALL treated with doxorubicin and also determined that event-free survival was unchanged after a median follow-up of 8.7 years [111–113]. Additionally, the Children's Oncology Group trials for localized and metastatic osteosarcoma whose patients received both doxorubicin and dexrazoxane showed no clinical evidence of cardiotoxicity [114,115].

One concern about dexrazoxane has been whether or not it reduces the oncologic efficacy of anthracycline therapy. To date, no definitive studies suggest that dexrazoxane decreases survival. In fact, a study of children and adolescents with nonmetastatic osteosarcoma who were treated with both dexrazoxane and doxorubicin showed that dexrazoxane did not compromise response to induction chemotherapy [116]. As well, in comparing 5-year event-free survival in patients on Pediatric Oncology Group Protocol POG 9404, there was no difference in survival between patients randomly assigned to treatment with or without dexrazoxane [112,113].

Another concern has been whether dexrazoxane is associated with or a cause of secondary malignant neoplasms (SMNs). Tebbi et al. reported in 2007 that dexrazoxane might have increased the risk of SMNs among children with Hodgkin's disease treated with doxorubicin, bleomycin, vincristine, and etoposide, with or without prednisone and cyclophosphamide [117]. Their findings ultimately led the European Medicines Agency in 2011 not to approve the use of dexrazoxane among children with cancer treated with anthracyclines [99]. Posted recommendations to the European Medicines Agency in 2017 recommended amending the 2011 decision, which is likely to occur. Tebbi's conclusion has been disputed, however, particularly because the study was not intended to determine whether SMNs were associated with dexrazoxane [118]. Since then, multiple studies have found that dexrazoxane is not associated with an increased risk of SMNs and has no adverse effect on overall long-term survival [110,119,120]. In fact, dexrazoxane may even help protect against SMNs associated with doxorubicin [121]. With very long-term follow-up of patients receiving dexrazoxane, dexrazoxane cardioprotection was maintained [122].

In a recent meta-analysis of randomized trials and nonrandomized observational studies with a pooled sample of 4639 children with cancer treated with an anthracycline, with or without dexrazoxane, dexrazoxane was associated with a statistically significant reduction in most cardiotoxic outcomes [123]. The authors also noted that the slightly higher risk of SMNs in patients receiving dexrazoxane was more likely to be related to the concurrent therapies than to dexrazoxane. Among the five randomized trials analyzed, SMNs occurred in 17 of 635 patients receiving dexrazoxane and 7 of 619 patients not receiving it. Importantly, only the two trials that treated patients with both etoposide and dexrazoxane found an increased rate of acute myelogenous leukemia. Only the one trial using cranial radiation reported an increased risk of secondary brain tumors among patients also receiving dexrazoxane. When these excess SMNs were removed from the analysis, there was no difference between groups [123]. Thus, much evidence supports the conclusion that dexrazoxane prevents cardiotoxicity without adverse outcomes in a wide range of cancers. The American Heart Association and the American Academy of Pediatrics have endorsed dexrazoxane for use as a cardioprotectant among children and adolescents undergoing anthracycline-containing protocols [54]. This has been used as the standard of good clinical care on all DFCI Childhood ALL Consortium protocols involving anthracycline therapy since 2000 and has been required to be written into all new COG protocols involving treatment with ≥150 mg/m^2 doxorubicin or anthracycline administration at any dose with planned radiation treatment portals that may impact the heart since 2015 [124].

There are certain other methods to prevent the cardiotoxicity caused by anthracyclines like analogs of anthracycline or changes to the anthracycline delivery system [55], which can be used, and are already approved in the adult population. These include:

(1) Liposomal anthracyclines: Liposomal encapsulation of doxorubicin helps to concentrate the drug in the tumor cells and hence reduces their concentration in blood [125,126]. The study by O'Brien et al. in adult patients with metastatic breast cancer revealed that treatment with liposomal formulation decreased the incidence of cardiotoxicity by fivefold while having comparable efficacy [127]. Another adult study on patients with breast cancer revealed similar results [128]. However, studies in pediatric patients are limited [129,130].
(2) Anthracycline analogs: Extensive pediatric studies comparing head-to-head efficacy of analogs versus

conventional anthracyclines have not been performed. However, they may be beneficial in reducing anthracycline cardiotoxicity, and further studies in this regard may be helpful. Analogs include:

(a) Epirubicin: An epimer of anthracycline that was introduced in the 1970s may be less cardiotoxic. However, a randomized clinical trial in pediatric soft tissue sarcoma patients involving 172 patients revealed no difference in the cardiotoxicity in both groups at a follow-up of 27.7 months (0% for epirubicin treated vs. 0.9% for doxorubicin treated) [131].
(b) Idarubicin: Another analog that was studied in a phase III trial revealed no difference in the incidence of heart failure between groups treated with idarubicin vs. daunorubicin [132].
(c) Mitoxantrone: This analog has a large volume of distribution and hence acts efficiently at the tissue level. A systemic review of published literature by van Dalen et al. [86] revealed that 0–6.7% patients had symptomatic mitoxantrone-induced cardiotoxicity and 0–80% had asymptomatic mitoxantrone-induced cardiotoxicity. They concluded that in order to confirm that mitoxantrone is less cardiotoxic than anthracyclines, a well-designed study should be undertaken.

However, the analogs and changes to the anthracycline delivery system's effectiveness in preventing toxicity in children have not been determined. Medications, such as ACEIs and beta-blockers, both used to treat HF and hypertension, among other disorders, can improve LV function in adults, but have not provided long-term improvements in children.

9. Expert opinion

The pediatric drugs are often known as 'therapeutic orphans' in the drug market [133]. Pediatric clinical trials are plagued with issues of recruitment, ethical considerations as well as low profitability, which mar their success [134]. The number of clinical trials enrolling children is far lower than for adults [135]. There is a serious dearth of pediatric drug development, and this has been acknowledged in the literature [136]. Breaking down silos across different disciplines is important, as there is a current need to improve pediatric pharmacotherapy and encourage collaborations between the community, industry, and the United States government.

The number of cancer survivors in the United States in 2012 was 12 million and this number is expected to double by the next decade [137]. Despite surviving their initial cancer, these survivors face considerable morbidity and mortality as adults due in part to the side effects of the chemotherapy they have received. Doxorubicin has been a widely used effective therapy in treating childhood cancers but it is now known to cause a myriad of complications like arrhythmias, cardiomyopathy and HF. Thus, it becomes important for physicians to detect these cardiotoxic effects of these medications with close monitoring and timely testing. Subclinical cardiac damage not evident on echocardiography can be detected by biomarkers like serum cTnT and NT-proBNP. Both the American Society of Echocardiography and European Society of Medical Oncology endorse the use of troponin for early recognition of the cardiotoxicity during chemotherapy [138]. Surveillance should begin early for these patients. The guidelines for the exact method, duration, and the frequency of the surveillance are currently controversial. So, further studies are needed to help delineate the best and uniform recommendations, which can then be used by clinicians in their daily practice. However, short of acute myocardial infarction levels of serum cTnT, it is not possible to make evidence-based decisions about withholding potentially lifesaving chemotherapy if there are elevations of serum levels of these cardiac biomarkers. No trial has been performed that compares conventional management versus cardiac biomarker guided management to see if the overall outcomes of morbidity, mortality, and quality of life are improved with cardiac biomarker-guided management.

Higher lifetime cumulative doses of anthracycline and higher dose rates are risk factors for late cardiotoxicity [139]. However, even doses as low as 250 mg/m^2 have been shown to cause cardiac damage, proving that there is not a cumulative dose of anthracycline that is free of late echocardiographic abnormalities in long-term survivors [58]. Unfortunately, no evidence-based specific therapy has been established as the standard-of-care for cardiac disease secondary to chemotherapy or radiation. Beta-blockers and ACEIs, for example, are standard-of-care medications for preventing and treating HF, but their effects on progression-free or overall survival, or even quality of life among survivors, have not been established [54], and the benefial effect of the ACEI enalapril in this population with either asymptomatic LV dysfunction or HF was transient, delaying but not preventing progression [85,98]. Their use in some survivors with restrictive cardiomyopathy may be detrimental and the fact that they exaccerbated inadequate LV hypertrophy may be concerning in their future [85,98]. Growth hormone replacement therapy increases LV wall thickness closer to normal but does not delay or prevent cardiomyopathy in survivors [84]. Thus, primary prevention of anthracycline cardiomyopathy is essential.

Less cardiotoxic analogs like epirubicin, as well as liposomal encapsulation of doxorubicin, which help to concentrate the drug in the tumor cells and decrease overall side effects, have shown some promise in treatment of the childhood cancers but have not been well studied. Cardioprotective medications have been a primary focus for preventing anthracycline-induced cardiotoxicity. Administering dexrazoxane with anthracycline chemotherapy, beginning before the first dose of anthracycline therapy, provides the best cardioprotection. In a recent long-term study, dexrazoxane proved to be very effective as a cardioprotectant and did not compromise antitumor efficacy or increase second malignancies [113].

There is often a building pressure on the pharmaceutical industry and the US FDA to expedite the approval of new drugs for faster improvement in clinical outcomes. However, if that is done, there should be a requirement for patients who received these drugs to participate in phase 4 confirmatory trials to establish their long-term safety and efficacy. When the US FDA grants an early approval to these drugs, there is often much less known about the long-term, multiorgan toxicity of these agents, especially when used in combination therapy.

For example, in adults, newer medications like immune checkpoint inhibitors have proven to improve clinical outcomes in various cancers like melanoma [140]. However, recent reports of fulminant myocarditis even with these new medications show that clinicians need to be extremely vigilant for cardiovascular toxicities even with these newer therapeutic agents [141]. Although these medications are currently used in adults, they will soon be utilized in the pediatric population. Reports like these, along with symptoms and functional surveys, may help to capture late toxicities from therapeutic agents in long-term survivors of childhood cancer.

According to the current estimates, the number of survivors of cancer is predicted to be about 20 million in the next decade [142]. This significant number warrants better understanding of the development of toxicities, effects of chronic toxicities by the various cancer therapeutic agents as well as 'tolerability' of these late toxic effects by the survivors. We need to learn the effects of possible treatment holidays, which may affect both toxicity and efficacy of cancer management. Often, patients with significant comorbidities or those who are heavily pretreated as high-risk patients in treatment regimens are often neglected or excluded in clinical trials. However, these are the patients who often develop severe toxicity. We need to add our patients as partners in our fight against cancer and engage them to grasp what is tolerable and acceptable by these survivors. Educating and engaging our patients will also help with treatment decisions and treatment adherence, which in turn improves outcomes. It is important to account for patient-reported outcomes or effects as the creation of this new feedback mechanism is critical and a potential opportunity for us to develop a better understanding of toxicity development.

There is a growing need for improving the preventive strategies for other side effects like HF in the treatment of childhood cancer. The National Institutes of Health has conducted a workshop, published a white paper, and established a funding mechanism (PA-16–035, PA-16–036) for the study of basic clinical research relevant to cardio-oncology [143]. The US National Cancer Institute's Provocative Questions initiative (PQ 9 specifically) and innovative seed funding programs such as the HESI-Pardee THRIVE Initiative provide funding to conduct research [144]. Using these resources, a huge network of expertise is developing to prevent, predict, and further manage treatment-related toxicities. There is a need to create new implementation initiatives, which include: (1) Sponsor studies and post-market surveillance. (2) New non-label adverse event reporting to the US FDA. (3) Label changes and usage changes. (4) Acute/chronic effects that impact adherence, morbidity, mortality, and quality of life.

With the recent advances in oncology, identification of driver mutations like Top2β, and deeper understanding of the mechanisms of the cardiotoxicities secondary to cancer therapy, we may be able to rapidly develop personalized cancer therapies based on the identification of these driver mutations [145]. These driver mutations may help predict sensitivities of certain patients to toxicities and thus help make decisions on the choice of therapy. This would enable the clinicians to be more proactive with symptom mitigation, and aid in considering alternative approaches or dosing schedules. Current research should focus on known knowledge, identifying remaining gaps, potential limitations of cancer therapy, and appropriate management of the toxicities. The available resources should focus on the scope of needed future research potential in the field of cardio-oncology and acknowledge the balance in managing and treating the adverse effects in this population in the absence of novel action and roles. This research has the potential to predict and recognize important mechanistic reasons of these toxicities, which may further lead to novel therapeutic mitigation strategies. There are exciting future opportunities in drug development and clinical medicine in the field of cardio-oncology as there is attainable room to improve long-term follow-up care to help survivors thrive post treatment.

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