Cardiotoxicity and Cardioprotection in Childhood Cancer

Steven E. Lipshultz^{a–c} Peter Sambatakos^{a, b} Michael Maguire^{a, b}
Ruchika Karnik^{a, b} Samuel W. Ross^{a, b} Vivian I. Franco^a Tracie L. Miller^{a, b}

^aDepartment of Pediatrics, University of Miami Miller School of Medicine, and ^bHoltz Children's Hospital, Jackson Health System, Miami, Fla., and ^cDepartment of Pediatrics, Wayne State University School of Medicine and Children's Hospital of Michigan, Detroit, Mich., USA

Key Words

Cardioprotection · Cardiotoxicity · Childhood cancer survivors

Abstract

Children diagnosed with cancer are now living longer as a result of advances in treatment. However, some commonly used anticancer drugs, although effective in curing cancer, can also cause adverse late effects. The cardiotoxic effects of anthracycline chemotherapy, such as doxorubicin, and radiation can cause persistent and progressive cardiovascular damage, emphasizing a need for effective prevention and treatment to reduce or avoid cardiotoxicity. Examples of risk factors for cardiotoxicity in children include higher anthracycline cumulative dose, higher dose of radiation, younger age at diagnosis, female sex, trisomy 21 and black race. However, not all who are exposed to toxic treatments experience cardiotoxicity, suggesting the possibility of a genetic predisposition. Cardioprotective strategies under investigation include the use of dexrazoxane, which provides short- and long-term cardioprotection in children treated with doxorubicin without interfering with oncological efficacy, the use of less toxic anthracycline derivatives and nutritional supplements. Evidence-based monitoring and screening are need-

ed to identify early signs of cardiotoxicity that have been validated as surrogates of subsequent clinically significant cardiovascular disease before the occurrence of cardiac damage, in patients who may be at higher risk.

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Introduction

In the 1970s, the 5-year survival rate of children diagnosed with cancer before the age of 15 years was less than 60% [1]. As of 2010, it is 83%, resulting in an estimated 379,000 survivors of childhood cancer in the USA [1, 2]. Although increased survival is promising, it is not free of consequences. These young survivors are in a developmental stage that makes them particularly vulnerable to adverse health effects from the potentially toxic anticancer treatments, which become apparent years later. More than 70% of childhood cancer survivors will experience a chronic health condition within the first 30 years after diagnosis [3]. Furthermore, cardiovascular-related disease is the leading cause of morbidity and mortality after cancer recurrence and secondary malignancies in these survivors [3–5]. By the age of 45 years, the cumulative incidence of coronary artery disease, heart failure,

valvular disease and arrhythmia among survivors is 5.3, 4.8, 1.5 and 1.3%, respectively, whereas the cumulative incidence for each among siblings is much lower: 0.9, 0.3, 0.1 and 0.4%, respectively [6].

Anthracyclines commonly used to treat hematological malignancies and solid tumors are effective but may cause persistent and progressive cardiovascular damage [7]. Furthermore, the risk increases when used in combination with radiation therapy [4, 8]. This review describes the mechanisms and course of anthracycline and radiation-induced cardiotoxicity and its risk factors in childhood cancer survivors, and discusses cardioprotective strategies to prevent or reduce long-term cardiac dysfunction.

Mechanisms of Anthracycline-Induced Cardiotoxicity

Anthracyclines, such as doxorubicin, epirubicin and daunorubicin, have substantially contributed to the improved cancer survival rates over the past 25 years in both adults and children [9]. These drugs have a range of anticancer properties that include preventing cell replication through DNA basepair intercalation and disrupting DNA uncoiling through inhibition of topoisomerase 2 activity. However, anthracyclines bind cellular membranes, which may negatively impact ion flow transport and form intracellular free radicals, which can further damage the cell [10].

Despite extensive research, the exact mechanism by which anthracyclines cause cardiotoxicity is still not fully known. Hypotheses include decreased ATP production as a consequence of decreased protein expression, impaired or destroyed mitochondria, and increased oxidative stress [10]. The oxidative stress hypothesis is the most commonly accepted hypothesis. Anthracyclines can form complexes with intracellular iron, which results in free radical formation, leading to the depletion of sulfhydryl-containing peptides, lipid peroxidation and DNA damage [10]. The heart is thought to be particularly sensitive to this stress as a result of an abundance of mitochondria in cardiomyocytes, which include high concentrations of cardiolipin. Cardiolipin's high affinity for anthracyclines allows the drugs to enter cardiomyocytes passively and accumulate in intracellular fluids to concentrations several hundred times higher than that in extracellular fluids [11]. Additionally, the heart has a reduced ability to scavenge free radicals created by the anthracyclines, given that there are lower concentrations than is normally present of catalase and glutathione peroxidase in the presence of

anthracyclines [10]. The increased stress and reduced free radical scavenging leads to cardiomyocyte-damaged DNA, reduced protein expression, damage to the cardiac sarcomere, destruction of myofilaments giving way to cell and organ damage, and left ventricular (LV) diastolic dysfunction with impaired contractility [9, 10].

Mechanisms of Radiotherapy-Induced Cardiotoxicity

Utilizing chemotherapy and radiation therapy together has been shown to improve oncological outcomes in many cancer patients, and about half of these patients now receive some amount of radiation [9]. However, much like the chemotherapeutic drugs, radiotherapy can also cause cardiotoxic side effects: myocardial fibrosis, cardiomyopathy, early coronary disease, and valvular and electrophysiological dysfunction [9]. The cardiotoxicity is believed to be caused by acute injury and inflammation leading to long-term myocardial fibrosis [10]. The risk of these cardiotoxic side effects increases two- to sixfold in patients receiving substantial chest radiation [12]. Cardiotoxicity from radiation is also dose dependent and correlates with the area of the heart exposed and the radiological technique used, as well as the patient's age, with a greater incidence in younger patients [9]. Patients receiving more than 1,500–3,500 cGy show an increased risk for cardiac disease, with high-level doses associated with myocardial ischemia as soon as 12 years after treatment [12].

Cardiotoxicity Risk Factors

Not every cancer survivor treated with anthracyclines and radiation experiences cardiotoxicity, but identifying risk factors may still help to determine which patients are at higher risk. These risk factors might help guide treatment and help clinicians determine appropriate follow-up intervals.

The risk of cardiotoxicity increases with a higher anthracycline cumulative dose. Cumulative doses greater than 500 mg/m² have been linked to early congestive heart failure [13]. In a study by Nysom et al. [14], after a median of 8.1 years since the end of anthracycline therapy, patients who received cumulative doses between 244 and 550 mg/m² experienced late anthracycline-related cardiotoxicity, as evidenced by depressed LV fractional shortening and increased LV dimension, whereas these conditions did not occur in 3 other cohorts who received

relatively lower doses (0–23, 45 and 73–301 mg/m²). According to another recent study in adolescent patients, about 13 years after treatment, subclinical events occurred in about 30% of the patients, even at doses of 180–240 mg/m² [15]. These findings suggest that there is no safe dose of anthracyclines. Even doses as low as 100 mg/m² have been associated with reduced cardiac function [14, 16, 17].

Younger age at diagnosis is also associated with anthracycline-induced cardiotoxicity [18, 19]. Children less than 4 years of age at anthracycline exposure showed an increased risk of LV dysfunction [7]. Females have a higher risk of anthracycline-induced cardiotoxicity than do males [20]. Also, survivors with trisomy 21 are at an increased risk for LV dysfunction, even when patients with congenital cardiovascular abnormalities are excluded [21]. A number of other risk factors exist as well that will not be covered here such as preexisting risk factors for or the presence of cardiovascular disease, and noncardiac medical conditions that increase the risk of cardiovascular disease, including but not limited to endocrinopathies, infections, inflammatory conditions, obesity and metabolic diseases, failure to thrive, sedentary lifestyle, pulmonary disease, musculoskeletal disease, renal disease, hepatic disease, concomitant or prior medication usage (licit and illicit), a history of ethanol, energy drink (stimulant), complementary and alternative therapies, and tobacco use, prior treatment for cancer, prematurity and genetic disorders. These should all be evaluated and considered prior to initiating cardiotoxic cancer therapies to identify high-cardiovascular-risk populations for treatment to reduce this risk by modification of these risk factors, using cardioprotective strategies, and by minimizing the use of, or avoiding, cardiotoxic cancer therapies.

Independently of these risk factors, not all children and adolescents exposed to toxic treatments, even those who receive the same standardized chemotherapeutic regimens, experience cardiotoxicity, suggesting the possibility of a genetic predisposition [20, 22, 23]. For example, hereditary hemochromatosis is a genetic disorder associated with a mutation of the *Hfe* gene, which encodes the human hemochromatosis protein, a protein that interferes with iron metabolism and leads to iron overload and increases susceptibility to anthracycline-associated toxicity [24]. An animal study in doxorubicin-treated mice showed that *Hfe* knockout mice (*Hfe*^{-/-}) displayed a higher degree of mitochondrial damage and iron deposits in the heart than did wild-type mice [24, 25].

As described above, anthracyclines form complexes with intracellular iron, which result in free radical forma-

tion; therefore, iron accumulating in the heart increases the susceptibility to doxorubicin-induced cardiotoxicity. In a recent study of long-term survivors of childhood high-risk acute lymphoblastic leukemia, 10% of survivors were carriers of a mutation in the C282Y allele, one of the mutations most commonly associated with *Hfe* [24]. Furthermore, the risk of myocardial injury in survivors who were heterozygous for the C282Y allele was 9 times higher than that in noncarriers [24]. Blanco et al. [26] found that among patients with single nucleotide polymorphisms in *CBR3* homozygous G genotypes (*CBR3:GG*), exposure to low-to-moderate doses of anthracyclines increased the risk of cardiomyopathy by 5 and 3 times that of survivors with the *CBR3:GA/AA* genotypes unexposed and exposed to low-to-moderate-dose anthracyclines, respectively. Polymorphisms in *CBR3* influence the synthesis of carbonyl reductases, which catalyze the reduction of anthracyclines to cardiotoxic alcohol metabolites [26]. These studies show the potential influence of genetics in identifying patients at an increased risk of anthracycline-induced cardiac effects; however, additional studies specifically designed to address and confirm these novel risk factors are needed.

Obesity is a well-known cardiac risk factor [27]. Compared with siblings, male survivors have a greater body fat and metabolic risk. Cranial irradiation and television hours are important risk factors for adiposity in pediatric cancer survivors [28]. In a study assessing the dietary trends of childhood cancer survivors, it was found that survivors consumed diets that only moderately adhered to current recommendations [29]. Dietary quality below current recommendations often leads to increased adiposity, increasing the risk for cardiovascular disease [29]. Targeting dietary consumption can decrease adiposity and lower cardiovascular risk. Furthermore, supervised physical activity should be encouraged to improve nutritional and cardiac conditions [30].

Klosky et al. [31] looked at childhood cancer survivors aged 14–20 years and found no significant difference between usage rates of tobacco, alcohol and illicit drugs, or risky sexual behavior when compared to sibling controls. Kahalley et al. [32] also found no significant difference in smoking rates between childhood cancer survivors and healthy sibling controls. However, Kahalley et al. did address the correlation between the increased incidence of smoking and health risk factors, such as peer smoking, household smoking and suicidal behavior. The risk factors noted by Kahalley et al., in addition to smoking, which is already an established risk factor for cardiovascular disease, put this patient popu-

lation into a high-risk group, and they should be counseled accordingly [33].

The sex of the patient also appears to be a risk factor for cardiotoxicity. Females have higher rates of LV dysfunction than do males exposed to similar doses of doxorubicin [34]. The cause of this increased risk associated with females is not clear. It is hypothesized that because doxorubicin does not reach a high concentration in adipose tissue, females generally have a higher percent body fat and anthracycline dosages are calculated based on body surface area, female cardiomyocytes may be exposed to a higher concentration when compared to cardiomyocyte intracellular concentrations in males [35].

Monitoring and Screening

Evidence-based monitoring and screening of childhood cancer survivors is imperative in identifying early signs of cardiotoxicity in patients who may be at higher risk. Aside from obtaining a thorough medical history, baseline cardiac studies are recommended before beginning chemotherapy [36–38]. Although endomyocardial biopsy may provide useful histological information, serial biopsies are not only expensive, but also highly invasive.

Newer studies of serum cardiac biomarkers are showing promise. These biomarkers may identify several different populations, including those experiencing cardiotoxicity, as well as those who may develop future cardiotoxicity. Lipshultz et al. [39] evaluated children with acute lymphoblastic leukemia treated with doxorubicin. They monitored concentrations of cardiac troponin T, N-terminal probrain natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein. Serum cardiac troponin T concentrations elevated in the first 90 days of treatment with anthracyclines were significantly associated with reduced LV end-diastolic posterior wall thickness, reduced LV mass and increased LV remodeling 4 years after therapy [39]. Serum NT-proBNP concentrations may indicate increasing LV wall stress, as this level rises with wall stretch. NT-proBNP concentrations were elevated in 89% of patients before treatment and in 48% of patients after treatment [39]. Overall, NT-proBNP was elevated in more patients than was cardiac troponin T, which may identify patients at risk for future cardiotoxicity, and significantly predicted late LV remodeling [39]. The authors did not find elevated high-sensitivity C-reactive protein concentrations measured during anthracycline therapy to be a reliable marker for patients who

may develop late cardiotoxicity as long-term survivors [39].

Additionally, as assessment of LV diastolic function and cardiac magnetic resonance imaging are increasingly used in pediatric cardiology, adolescent patients may benefit from its ability to identify cardiotoxicity. However, limited availability of diastolic function measurements and the availability, accessibility, high cost and lengthy studies may potentially limit widespread cardiac magnetic resonance usage.

Preventing Cardiotoxicity

Given the risk of cardiotoxicity with anthracyclines, various strategies to limit cardiac injury without reducing oncological efficacy have been explored. These are summarized below.

Continuous versus Bolus Anthracycline Infusion

In adults, cardiotoxicity assessed early after anthracycline infusion is reduced by continuous infusion, which lowers peak plasma levels in comparison with bolus infusions [40]. However, these same results were not replicated in a large prospective randomized controlled trial of children with a diagnosis of high-risk acute lymphoblastic leukemia [41]. Neither outcome with LV function nor 10-year event-free survival differed significantly between groups receiving either continuous or bolus infusion [41, 42]. This study suggests that continuous infusion of anthracyclines does not provide cardioprotection over bolus infusion in children [41].

Structural Modifications of Anthracyclines

Modifying the structural form of anthracyclines to reduce their cardiotoxicity is another experimental approach. Epirubicin, a structural analog of doxorubicin, has less overall toxicity but the same efficacy as doxorubicin. A cumulative dose of epirubicin up to 900 mg/m² is equivalent to only 450 mg/m² of doxorubicin in terms of cardiotoxicity [43].

Two separate studies of patients with breast cancer showed that epirubicin had a less toxic profile than doxorubicin [44, 45]. A meta-analysis of 5 randomized control trials comparing epirubicin to doxorubicin found no significant difference in the incidence of early clinical heart failure between control and experimental groups [46]. However, on the basis of a wide confidence interval and a low relative risk, this meta-analysis suggested a lower rate of clinical heart failure in the epirubicin treatment

group [46]. All these studies were limited to adults with solid tumors. Response rates did not differ between groups [46]. In a separate study, also in adults, lower doses of epirubicin up to 360 mg/m² have also caused subclinical cardiotoxicity [47].

Other doxorubicin analogs, idarubicin and mitoxantrone, although they may reduce cardiac injury, do not completely eliminate the risk of cardiotoxicity [43, 48]. Studies with use of these different analogs have so far been done only in adults with breast cancer [47, 48]. To our knowledge, no studies have been conducted in adolescents that might justify the use of analogs in this group.

Liposomal Anthracyclines

Liposomal anthracyclines have a better and safer oncological profile than do conventional anthracyclines [49]. Two forms of liposomal anthracyclines are currently available: pegylated PL-ODX/Doxil/Caelyx and non-pegylated TI-D99/Myocet.

Pegylated anthracyclines, compared to regular anthracyclines, have longer circulation times, longer half-lives, slower clearance from plasma, a smaller volume of distribution and they cannot penetrate cardiac cell tight junctions [50, 51]. These characteristics result in higher drug concentrations in tumors and lower concentrations in the heart [51]. Therefore, pegylated anthracyclines decrease cardiotoxicity while maintaining oncological efficacy. This conclusion was supported by endomyocardial biopsies of patients receiving liposomal versus conventional anthracyclines [49].

Another retrospective study showed that cumulative doses of the pegylated form, up to 500 mg/m², did not result in heart failure [52]. A meta-analysis of 2 other randomized controlled trials in women with metastatic breast cancer found fewer clinical and subclinical cardiac events in the group receiving liposomal anthracyclines [46]. However, no randomized controlled trials in children have been conducted to reproduce these results [51].

Only 1 randomized trial studied the use of liposomal daunorubicin as a second-line therapy in children with relapsed acute myeloid leukemia [53]. However, interpreting cardiac damage in this population is difficult because the patients had already undergone aggressive first-line therapy.

Use of Cardioprotective Agents

Dexrazoxane

Dexrazoxane is an iron-chelating agent that reduces the formation of iron-anthracycline complexes [54, 55]. Without these iron-anthracycline complexes, the genera-

tion of reactive oxygen species is limited, thus limiting the toxicity of anthracyclines [54, 55]. Dexrazoxane also interferes with topoisomerase 2 β , thereby antagonizing doxorubicin-induced DNA damage [56].

A randomized controlled trial by Lipshultz et al. [54] compared children less than 18 years of age with a diagnosis of high-risk acute lymphoblastic leukemia receiving doxorubicin alone with those receiving treatment with dexrazoxane and doxorubicin. The cardiac damage, as measured by serum cardiac troponin concentrations, was significantly less in the group receiving dexrazoxane [54]. Girls treated with doxorubicin and dexrazoxane had better long-term outcomes in terms of LV fractional shortening, LV end-diastolic dimension, LV posterior wall thickness and LV pathological remodeling measurements [55]. At the same time, the rate of secondary neoplasms and 8-year event-free survival was similar, whether or not children received dexrazoxane with doxorubicin [55].

A meta-analysis by Van Dalen et al. [57] revealed statistically lower rates of heart failure in children and adult patients who had been treated with dexrazoxane when compared to those who had not. The two groups did not differ significantly in antineoplastic effects or in survival rates [57]. The American Society of Clinical Oncology recommends dexrazoxane in adult patients with metastatic breast cancer being treated with anthracyclines in cumulative doses greater than 300 mg/m² [58].

Carvedilol

Carvedilol provides cardioprotection by inhibiting reactive oxygen species, scavenging free radicals, preventing lipid peroxidation and increasing vitamin E concentrations [59]. Some of these mechanisms have been documented in in vitro studies [60]. Carvedilol reduced anthracycline-induced cardiomyopathy in rats [61]. This evidence further needs to be supported in human studies [61].

Supplements

Coenzyme Q

Coenzyme Q, an antioxidant, is an important part of the mitochondrial respiratory chain [62]. Supplementation of coenzyme Q prevented anthracycline-induced cardiotoxicity in both preclinical and clinical studies [62]. Currently, only 1 study has shown that coenzyme Q treatment has reduced the incidence of cardiotoxicity in children treated with doxorubicin [63].

L-Carnitine

The naturally occurring amino acid L-carnitine protects the heart from damage by its antioxidant action against an-

Fig. 1. Potential opportunities for targeted multiagent 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 reactive oxygen species. Furthermore, it impairs Ca^{2+} processing in the sarcoplasmic reticulum and inhibits the transcription of important muscle elements, weakening the heart muscle. It also downregulates adrenergic receptors and interrupts cell signaling. We have explored 4 areas for multiagent anthracycline cardioprotection, but other mechanisms and potential targets exist as well. This figure illustrates the 4 areas we have fo-

cused on and their potential cardioprotective mechanisms and includes: (1) administration of dexrazoxane, which can prevent Fe^{2+} complex formation; (2) intravenous immunoglobulin therapy, which can reduce inflammatory cytokines; (3) L-carnitine, which can bolster mitochondrial function, and (4) anti-heart-failure therapies, such as angiotensin-converting enzyme inhibitors and β -blockers, which can prevent further damage and pathological ventricular remodeling. cTn = Cardiac troponin; MLC2 = myosin light chain 2; MM-CK = myofibrillar isoform of the creatine kinase enzyme; NO = nitric oxide; ROS = reactive oxygen species; TOP2 = topoisomerase 2. Modified with permission from Lipshultz et al. [70] in Nature Publishing Group.

thracycline-induced lipid peroxidation of cardiac membranes and by reducing the ability of anthracyclines to inhibit long-chain fatty acid production [58]. Therefore, L-carnitine supplementation should protect against the acute and chronic effects of anthracycline-induced cardiotoxicity. However, there is insufficient evidence to justify the conclusion that L-carnitine is cardioprotective [46, 64].

Glutathione

Glutathione, a tripeptide thiol, is another antioxidant that scavenges free radicals. It acts as a substrate for glutathione peroxidase whose activity is interfered with by anthracyclines [65]. Thus, glutathione supplementation may protect the heart from anthracycline effects [58]. Both in vitro and animal studies have shown that gluta-

thione supplementation decreases cardiac damage [66–69]. Glutathione does have potential in preventing anthracycline-induced cardiac damage.

Conclusion

Advancements in cancer therapies have undoubtedly contributed to the improved life expectancy of childhood cancer survivors. However, despite this increased survival, many survivors have a lower quality of life as a result of the adverse late effects of the same treatments that cured their cancer. Exposure to these treatments of children at a young age makes them particularly vulnerable to impaired growth and development and to an increased risk of premature cardiovascular disease. Screening for risk factors, including genetic risk factors such as *Hfe*,

together with serum biomarkers, might prove useful at early stages to inform treatment decisions. However, the mechanisms of anthracycline- and radiation-induced cardiotoxicity need to be better understood to develop effective and safe cardioprotective strategies. Nevertheless, an effective cardioprotective agent, dexrazoxane, has been validated in children receiving anthracycline chemotherapy and should be incorporated into clinical trials where children with cancer receive anthracycline chemotherapy. Additional cardioprotective strategies may allow for multiagent cardioprotection to maximize oncological efficacy while minimizing toxicity and late adverse effects (fig. 1). This is particularly important since the successful treatment of childhood cancer brings about the overall quality of life during a lifespan as determined by the balance between efficacy and late effects.

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