Prevention of cardiotoxicity among survivors of childhood cancer

Kelley K. Hutchins¹, Hani Siddeek², Vivian I. Franco³ and Steven E. Lipshultz³,⁴

¹Department of Pediatric Hematology/Oncology, Children’s Hospital of Michigan, 3901 Beaubien Boulevard, Detroit, Michigan 48201, USA, ²Department of Pediatrics, Children’s Hospital of Michigan, 3901 Beaubien Boulevard, Detroit, Michigan 48201, USA, ³Department of Pediatrics, Wayne State University School of Medicine, 3901 Beaubien Boulevard, Suite 1K40, Detroit, Michigan 48201, USA, and ⁴Karmanos Cancer Institute, Children’s Hospital of Michigan

Keywords cardiotoxicity, childhood cancer, dexrazoxane, survivor

The number of survivors of childhood cancers has increased exponentially over the past few decades. However, these survivors are also at substantially increased long-term risk of morbidity and mortality, especially from treatment-related cardiotoxicity. Preventing these risks is now a priority when treating children and adolescents with cancer. Dexrazoxane reduces the risk of anthracycline-induced cardiotoxicity among adults and children with cancer without reducing its antineoplastic effects or event-free survival. Thus, it should be strongly considered as a part of therapy for children and adolescents treated with anthracyclines.

Tables of Links

<table>
<thead>
<tr>
<th>TARGETS</th>
<th>LIGANDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCC5</td>
<td>HER2</td>
</tr>
<tr>
<td>NOS3</td>
<td></td>
</tr>
<tr>
<td>BNP</td>
<td>Enalapril</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Etoposide</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>Fluorouracil</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>IGF-1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Dexrazoxane</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Vincristine</td>
</tr>
</tbody>
</table>

These Tables lists key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

© 2016 The British Pharmacological Society DOI:10.1111/bcp.13120
**Introduction**

Survival rates of childhood cancers have substantially improved over the past several decades as a result of new and improved treatments. The overall 5-year survival rate has increased from 58% in the mid-1970s to 83% today [4]. Acute lymphoblastic leukaemia (ALL) alone has an overall cure rate between 85% and 90% [5]. As a result of increased survival, however, these patients are at an increased risk of adverse treatment-related effects. For example, chemotherapeutic agents such as anthracyclines and radiation therapy are extremely effective against numerous types of cancer, but they are also cardiotoxic.

Survivors of childhood cancer are at a significantly higher risk of cardiovascular morbidity and mortality as a result of treatment. Most of these survivors will experience one or more chronic health condition within 30 years of their diagnosis [6]. These findings have been verified in numerous large-scale, multicentre studies including randomized controlled trials. For example, the Childhood Cancer Survivor Study reported that the overall mortality rate in survivors of childhood cancer is 8.4 times higher than that of healthy controls [7]. Recurrence and progression of the underlying disease account for almost 60% of the deaths in these patients, followed by secondary cancers (19%), circulatory diseases (7%), and respiratory diseases (3%) [7]. The British Childhood Cancer Survivor Study also noted excess long-term mortality from secondary primary malignancies, as well as circulatory disease, 25 years after the initial cancer diagnosis [8]. In addition to the need to improve event-free and overall survival in these patients, these findings support the need to focus on late effects as well as on quality of life. Therefore, preventing cardiotoxicity is of utmost importance in survivors of childhood cancer.

**Effects of anthracycline-related cardiotoxicity**

Several treatments effectively manage and even cure various forms of paediatric cancer. With these treatments, however, come numerous adverse effects. Anthracyclines (e.g., doxorubicin, daunorubicin, and epirubicin) are among the most commonly used chemotherapeutic agents for treating children with any of several haematological and solid tumour malignancies. These drugs are unfortunately associated with well-known cardiac conditions resulting from the irreversible and dose-dependent loss of cardiomyocytes [9–11]. Cardiotoxic effects include, but are not limited to, cardiomyopathy (initially dilated cardiomyopathy that may then progress to a restrictive cardiomyopathy), heart failure, myocardial infarction, conduction defects, valve disease, pericardial disease, and hypertension (Figure 1) [12–15]. An anthracycline cumulative dose of 300 mg m$^{-2}$ or greater substantially increases this risk. However, subclinical echocardiographic abnormalities were found among patients treated with a cumulative dose of anthracyclines <100 mg m$^{-2}$ [16], indicating that there is no safe dose of these drugs [11, 17].

Anthracycline-associated cardiotoxicity reduces left ventricular (LV) wall thickness and mass, as well as LV fractional shortening [9, 12, 13]. In survivors of malignant bone tumors treated with anthracyclines, after 22 years of follow-up, adverse cardiac structural changes ultimately resulted in marked, progressive cardiac dysfunction [18]. A cross-sectional study by the Dana–Farber Cancer Institute evaluated serial echocardiograms (n = 499) from long-term survivors of childhood acute lymphoblastic leukaemia treated with doxorubicin (n = 115) [13]. The median follow-up after completion of therapy was 11.8 years. Patients initially developed asymptomatic dilated cardiomyopathy soon after the completion of doxorubicin therapy as diagnosed by reductions in LV fractional shortening and contractility with LV dilation. Over time, this cardiomyopathy normalized but years later progressed to a restrictive cardiomyopathy diagnosed by significantly reduced LV wall thickness, fractional shortening and contractility with normal to reduced LV dimension (Figure 1) [13]. Compared to their healthy siblings, survivors have up to five times the risk of heart failure, valvar disease, and pericardial disease. In addition, up to half of all survivors treated with anthracyclines will experience some form of cardiac dysfunction within 20 years after anthracycline treatment [18]. Given the young age of this population at the time of diagnosis and treatment, survivors of childhood cancer are especially vulnerable to these risks at an early age.

![Figure 1](image-url)
Risk factors for anthracycline-related cardiotoxicity

Survivors of childhood cancers are at the same risk for developing atherosclerotic disease as the general population. Unfortunately, those with a history of anthracycline treatment are at greater risk for cardiotoxicity because of the drugs’ inherent adverse effects against cardiomyocytes. Risk factors such as age, body weight, female sex, radiotherapy, trisomy 21, genotype or phenotypic evidence of or susceptibility for preexisting cardiomyopathy, genotypic evidence of increased cardiotoxic risk from anthracycline chemotherapy, diabetes, hypertension, and others are examples of why a careful patient assessment prior to treating with anthracyclines is advised. Risk factors of anthracycline-related cardiotoxicity include treatment-related and both modifiable and nonmodifiable risk factors (Table 1).

### Therapy-related risk factors

A high cumulative dose of anthracyclines is the most important risk factor for cardiotoxicity among survivors [11]. The risk of cardiotoxicity at cumulative doses $>300 \text{ mg m}^{-2}$ is 11 times as high as at cumulative doses $<300 \text{ mg m}^{-2}$ [11, 19, 20]. Despite this increased risk, however, cardiotoxicity can develop at cumulative doses $<240 \text{ mg m}^{-2}$ [11, 21].

Concomitant mediastinal or cranial radiation is an additional risk factor for cardiotoxicity [22]. Among 294 survivors of Hodgkin lymphoma exposed to mediastinal radiation, 23

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Risk factors for anthracycline-related cardiotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factors</strong></td>
<td><strong>Comment</strong></td>
</tr>
<tr>
<td>Cumulative anthracycline dose</td>
<td>Cumulative doses $&gt;300 \text{ mg m}^{-2}$ are associated with significantly elevated long-term risk</td>
</tr>
<tr>
<td>Time after therapy</td>
<td>The incidence of clinically important cardiotoxicity increases progressively over decades</td>
</tr>
<tr>
<td>Rate of anthracycline administration</td>
<td>Continuous infusion not cardioprotective in children</td>
</tr>
<tr>
<td>Individual anthracycline dose</td>
<td>Higher individual doses are associated with increased late cardiotoxicity, even when cumulative doses are limited; no dose is risk-free</td>
</tr>
<tr>
<td>Type of anthracycline</td>
<td>Liposomal encapsulated preparations may reduce cardiotoxicity. Data on anthracycline analogues and differences in cardiotoxicity are conflicting</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>Cumulative cardiac radiation dose $&gt;30 \text{ Gy}$ before or concomitant with anthracyline treatment; as little as $5 \text{ Gy}$ increased the risk</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td>Trastuzumab, cyclophosphamide, bleomycin, vincristine, amonaxtrone, among others, may increase susceptibility or toxicity</td>
</tr>
<tr>
<td>Preexisting cardiac risk factors</td>
<td>Hypertension; ischemic, myocardial and valvular heart disease; prior cardiotoxic treatment</td>
</tr>
<tr>
<td>Personal health habits</td>
<td>Smoking; consumption of alcohol, energy drinks, stimulants, prescription and illicit drugs</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Diabetes, obesity, renal dysfunction, pulmonary disease, endocrinopathies, electrolyte and metabolic abnormalities, sepsis, infection, pregnancy, viruses, elite athletic participation, low vitamin D concentrations</td>
</tr>
<tr>
<td>Age</td>
<td>Young (&lt;1 year) and advanced age at treatment are associated with elevated risk</td>
</tr>
<tr>
<td>Sex</td>
<td>Females are at greater risk than males</td>
</tr>
<tr>
<td>Complementary therapies</td>
<td>More information needs to be collected to assess risk</td>
</tr>
<tr>
<td>Additional factors</td>
<td>Trisomy 21; African–American ancestry</td>
</tr>
</tbody>
</table>

had coronary events after 6.5 years of follow-up, of which 10 were myocardial infarctions [23]. Cranial radiation has been associated with cardiovascular disease—specifically decreased LV mass—presumably in part through its detrimental effect on the hypothalamic and pituitary glands that lead to growth hormone deficiency [14, 24–27]. It is not clear whether the effect of cranial radiation on cardiotoxicity is additive or synergistic with anthracycline treatment [28]. Longer follow-up and greater cumulative doses of anthracycline increase the prevalence of cardiotoxicity in survivors; however, evidence of cardiotoxicity after relatively shorter follow-up times is possible [17].

**Nonmodifiable risk factors**

Independent of the aforementioned therapy-related risk factors, some patients appear to be inherently more susceptible to cardiotoxicity. For example, not all children exposed to anthracyclines will experience LV dysfunction or other forms of cardiac dysfunction, suggesting a possible genetic predisposition [29–34]. Krajnovic et al. [31] identified two genes that may modulate late-onset chronic cardiotoxicity among children with ALL treated with doxorubicin. Patients with an A-1629 T genotype variant in the ABC5 gene, an ATP-binding cassette transporter gene, had significant decreases in LV ejection and shortening fractions, suggesting impairment of cardiac function. By contrast, patients with a G-894 T genotype variant of the NOS3 gene, an endothelial nitric oxide synthase gene, demonstrated an increase in the LV ejection fraction, suggestive of a potential protective effect [31].

Mutations of the haemochromatosis gene (HFE), which is associated with hereditary haemochromatosis, interfere with iron metabolism, leading to iron overload and consequently increased susceptibility to anthracycline-related cardiotoxicity [32]. In one study of 184 survivors of childhood ALL, 10% carried a mutation in the HFE C282Y allele. Those who were heterozygous for the HFE C282Y mutation had a nine-fold higher risk of myocardial injury than that of non-carriers [32]. In an additional study, patients homozygous for the G allele in CBR3, a gene that encodes for carbonyl reductase 3, were at increased risk of cardiomyopathy when exposed to low-to-moderate doses of anthracyclines [29]. Such genetic predispositions may allow for genetic screening as well as guiding treatment of susceptible patients.

Children with pre-existing cardiovascular disease or a family history of premature cardiovascular disease are at an increased risk of cardiotoxicity after anthracycline treatment [32]. Additionally, females are more vulnerable than males to anthracycline-induced cardiotoxicity at the same cumulative anthracycline dose [35]. One likely explanation for this sex-related difference is that females have a higher percentage of body fat. Having a greater percentage of body fat could contribute to a higher incidence of cardiac damage because anthracyclines are poorly absorbed by fat. Therefore, at the same dose, females will have higher circulating concentrations that increase the effective dose to cardiomyocytes [35].

Younger age at diagnosis is also associated with increased risk of anthracycline-related cardiotoxicity. Specifically, the risk is elevated for increased LV afterload and decreased LV mass and LV wall thickness [35]. Patients with trisomy-21 and African–Americans are also at increased risk of early anthracycline-related cardiotoxicity [36].

**Modifiable risk factors**

Patients treated with anthracyclines are likely to be subject to incremental cancer and its therapy related risks, as well as to conventional risks for atherosclerotic disease found in the noncancer population. A rigorous initial cardiovascular assessment followed by close monitoring is advised. Nonpharmacological measures such as exercise, healthy lifestyles, control of risk factors and treatment of comorbidities may be helpful in this population at high risk for premature cardiovascular disease. Addressing modifiable risk factors, such as physical inactivity, hypertension, diabetes, obesity and smoking may be important in reducing the incidence of atherosclerosis and hypertensive cardiovascular disease in survivors of childhood cancer similar to the general population [37]. Although the Centers for Disease Control and Prevention recommend that children aged 6–17 years should be physically active for at least 60 minutes a day [38], childhood cancer survivors are more likely to report having an inactive lifestyle than their healthy counterparts when matched for age and sex [39]. Additionally, survivors also report watching more television than their siblings [39, 40]. Among older childhood cancer survivors, a higher percentage of body fat, a history of methotrexate treatment, and either high or low LV mass were associated with lower maximum oxygen consumption [40]. In females, maximum myocardial oxygen consumption was lower than that of their sibling controls [41].

Childhood obesity is epidemic in the USA, and survivors of childhood cancer are at an especially high risk, given their sedentary lifestyle [40]. Miller et al. [40] found that male survivors had a higher percentage of body fat and truncal obesity than that of their siblings and were more likely to be overweight or obese. Although survivors are at greater risk, the prevalence of obesity in childhood cancer survivors is currently similar to that of the general population [42]. One study of 7195 childhood cancer survivors found that 13% were obese and 28% were overweight [43]. An additional study found that about a third of 441 cancer survivors were obese or overweight [44].

Survivors exposed to cranial irradiation were at increased risk of cardiotoxicity through its detrimental effects on the hypothalamus and pituitary glands and subsequent deficiency in growth hormone. These survivors also had substantially lower insulin-like growth factor-1 concentrations than those of unexposed survivors, placing them at greater risk for obesity [24]. Obesity may increase the risk of cardiotoxicity in survivors because their cardiovascular systems might not be able to compensate for the conditions associated with obesity, such as ischemia or atherosclerosis.

Obese survivors of childhood cancer with sedentary lifestyles are at additional risk for insulin resistance and diabetes mellitus. This risk is especially present in survivors treated with hematopoietic stem cell transplantation. In one study of these survivors, the 10-year cumulative incidence of diabetes was 18% [44]. In an analysis of National Health and Nutrition Examination Survey data, Armenian et al. also noted that between 1995 and 2008, the prevalence of diabetes developing in survivors treated with stem cell transplantation
increased from 8% to 17% in survivors but only from 6% to 9% in the general population [44]. In another study of 7195 long-term survivors of childhood cancer by Meacham et al. [45], diabetes was twice as likely to develop in survivors as it was in the general public. Radiation to the abdomen, head, and total body was associated with an even higher incidence of diabetes. Finally, a prospective study of 248 childhood cancer survivors found that, over a 13-year period, 4% had diabetes, 4% had hyperinsulinemia, and 7% had glucose intolerance [46].

Although the rate of smoking among cancer survivors is less than that of the general population (17% vs. 20%, respectively) [47], smoking cessation is of utmost importance to long-term survival. The prevalence of illicit drug use among childhood cancer survivors is similar to that of the general population, but additional general health education should be implemented in this susceptible population due to the cardiotoxic effects of these substances [48]. Shultz et al. [49] found that of 117 survivors of acute myeloid leukaemia aged 18 years or older, 25% reported binge drinking, and less than 10% reported cocaine, heroin, or methamphetamine use. Males were more likely to abuse drugs than were females. Given that alcohol and cocaine are both risk factors for cardiomyopathy in the general population (Shultz et al., 2010), abuse is especially concerning among patients with anthracycline-mediated cardiomyopathy.

Preventing anthracycline-induced cardiotoxicity: dexrazoxane

Dexrazoxane can prevent late effects from anthracycline treatment. Studies on beagles in the early 1980s first documented dexrazoxane’s ability to reduce chronic doxorubicin cardiotoxicity [50]. It is believed to chelate iron and therefore interferes with iron-mediated free radical generation, ultimately decreasing tissue damage caused by anthracyclines (Figure 2) [14, 51]. Hasinoff et al. [52] recently examined the ability of dexrazoxane to protect against myocyte damage...
from doxorubicin when combined with either bortezomib or carfilzomib, proteasome inhibitors also known to be cardiotoxic. Dexrazoxane maintained its cardioprotective effects supporting the hypothesis that its mechanism acts by preventing iron-based doxorubicin-mediated oxidative stress and establishing that its cardioprotective effects were not exclusively due to targeting of topoisomerase II-beta. Doxorubicin targets mitochondria and dexrazoxane abrogates these effects [53]. Mitochondrial transcription in energy metabolism and apoptosis genes were significantly altered by doxorubicin administration but these changes were attenuated by pretreatment with dexrazoxane [54]. Clinical trials conducted among women with breast cancer established its cardioprotective effectiveness in humans [55]. Dexrazoxane is given at a 10:1 ratio by intravenous infusion immediately before anthracycline administration. Speyer et al.’s. [56] randomized controlled trial included 150 women with advanced breast cancer treated with fluorouracil, doxorubicin and cyclophosphamide with or without dexrazoxane (ICRF-187) and demonstrated a significant difference in incidence of clinical heart failure between the two groups (two patients in the ICRF-187 compared to 20 in the control group). The use of dexrazoxane for anthracycline cardioprotection has been determined to be cost effective in several studies [57–61].

Since its approved use in women with breast cancer treated with anthracyclines, multiple clinical studies have found that dexrazoxane prevents cardiotoxicity among children and adolescents. Importantly, dexrazoxane is cardioprotective without decreasing the effectiveness of anthracyclines or compromising event-free survival. Its use as a cardioprotectant among children and adolescents has also been endorsed by the American Heart Association and the American Academy of Pediatrics [62]. A randomized, multicentre trial conducted by the Dana–Farber Cancer Institute’s Childhood ALL Consortium Protocol 95–01 found that dexrazoxane was associated with a decrease in cardiac injury among children with ALL treated with doxorubicin [63]. Patients were assigned to receive either doxorubicin with dexrazoxane or doxorubicin alone. Serum concentrations of cardiac troponin T, a well-known marker for acute myocardial injury, were significantly higher in patients treated with doxorubicin than in those who also received dexrazoxane. Furthermore, at a median follow-up of 2.7 years, event-free survival did not differ significantly. Additional long-term results from this same multicentre trial revealed that dexrazoxane provides long-term cardioprotection, as determined by echocardiography, 5 years after completing doxorubicin chemotherapy with no significant difference in event-free survival at 8.7 years of follow-up [64].

Three large, consecutive, multicentre randomized control trials have studied the incidence of secondary malignant neoplasms (SMNs) among patients with high-risk ALL treated with dexrazoxane and doxorubicin [65]. After a median follow-up of 3.8 years, only one SMN was observed among 553 patients. A recent report from the Children’s Oncology Group concluded that dexrazoxane had no adverse effect on overall long-term survival among patients with T-cell ALL, T-cell acute lymphoblastic lymphoma, or low-, intermediate-, or high-risk Hodgkin lymphoma after a median follow-up of 12.6 years (Figure 3) [66].

Furthermore, the Pediatric Oncology Group 9404 randomized trial found that dexrazoxane was cardioprotective among children and adolescents with newly diagnosed T-ALL or lymphoblastic non-Hodgkin lymphoma without compromising antitumour efficacy [67]. Additionally, this study also noted that dexrazoxane was not associated with an increased incidence of SMNs or toxicities.

Studies of children with osteosarcoma have also documented the effectiveness of dexrazoxane in combination with anthracyclines to prevent cardiotoxicity [68, 69]. In a phase II trial among patients with HER2-positive metastatic osteosarcoma, combining trastuzumab with doxorubicin and dexrazoxane did not increase the risk of acute myocardial injury [68]. Schwartz et al., in patients with nonmetastatic osteosarcoma, found that dexrazoxane allowed doxorubicin therapy to be intensified without impairing tumor response or increasing the risk of SMNs [69].

Tebbi et al. [70] suggested that, in patients with low- and high-risk Hodgkin lymphoma, dexrazoxane might increase the incidence of SMNs when added to standard treatment of doxorubicin, bleomycin, vincristine and etoposide (ABVE), or dose-intensified ABVE with prednisone and cyclophosphamide followed by low-dose radiation. Their conclusions were based on the results of Pediatric Oncology Group trials 9426 and 9425, in which 10 SMNs occurred among 478 patients randomly assigned to treatment with or without dexrazoxane. Based on these results the European Medicines Agency’s Committee for Medicinal Products for Human Use reported in 2011 that dexrazoxane may be associated with SMNs in children [71]. However, the statistical evidence of their findings was limited because the study was not designed to examine SMNs and dexrazoxane use, and several trials have also found that dexrazoxane has not been associated with an increase in SMNs [72]. In fact, some studies have suggested that dexrazoxane may avert SMNs by reducing doxorubicin-
induced aneuploidy in part by its free radical reducing activity [73]. Further, preclinical studies of dexrazoxane have not shown interference with the anticancer activity of doxorubicin or trastuzumab [74]. The EMA should therefore re-evaluate the safety and efficacy of dexrazoxane as a cardioprotective medication against anthracycline-induced cardiotoxicity for children and adolescents.

Preventing anthracycline-induced cardiotoxicity: other treatment options

Various medical therapies and techniques have been studied in an attempt to prevent or mitigate anthracycline-induced cardiotoxicity. Several potentially cardioprotective agents other than dexrazoxane have been developed and tested in animals in small clinical trials but await large scale clinical trials including statins, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, angiotensin receptor antagonists, liposomal formations of anthracyclines, and beta-adrenergic antagonists. In particular, several studies have tested ACE inhibitors. Enalapril, an ACE-inhibitor commonly used to treat heart failure, LV dysfunction, and hypertension, has been studied among children with cancer treated with anthracyclines. An observational study found that enalapril delayed the progression of cardiotoxicity among survivors but did not prevent its progression [75]. In a randomized, double blind, placebo-controlled trial of survivors of childhood cancer, enalapril also improved LV wall stress but did not affect overall exercise tolerance among the participants [76]. The beta-blocker carvedilol, which is also used to treat heart failure, hypertension, and LV dysfunction after myocardial infarction among other conditions, is currently being studied to assess its potential in preventing heart failure among survivors of childhood cancer treated with anthracyclines (NCT02717507) [88]. More studies are needed to assess whether additional medications may be cardioprotective in patients treated with anthracyclines.

Administering doxorubicin as a continuous infusion to lower peak blood concentrations has also been tested to prevent anthracycline-induced toxicity in children and adolescents. The Dana–Farber Cancer Institute’s ALL Consortium Protocol 91–01 compared continuous 48-hour infusion to bolus dosing of doxorubicin among patients with high-risk ALL [25]. Both groups had marked abnormalities in LV structure and function from baseline after a median of 8 years of follow-up. However, neither measures of cardiac function or event-free survival differed between the two groups. Although doxorubicin administered continuously provides early cardioprotection in adults, its administration to protect the heart as a continuous infusion is not supported over bolus dosing in children and adolescents [25, 75, 77–79].

Additional cardioprotective techniques may include further decreasing the total cumulative dose of anthracycline or eliminating its use altogether. Given the additive adverse effects of radiation treatment, reducing or eliminating radiation exposure would also be ideal. Although these techniques can reduce cardiotoxicity, their benefits need to be balanced with any potential adverse effects and reductions in efficacy. Research is needed to determine how to reduce or potentially replace these techniques with newer, less-toxic treatments that remain equally effective.

Follow-up and monitoring of survivors with cardiotoxicity

Early detection of adverse effects, such as cardiotoxicity from cancer therapy, is necessary to be able to intervene quickly and effectively. Organizations, such as the Children’s Oncology Group, have developed consensus-based recommended guidelines for detecting adverse health effects among survivors of childhood cancer [80]. Despite existing recommendations, studies are needed to establish more validated, evidence-based guidelines for monitoring this population [14].

Recommendations for cardiotoxicity screening among childhood cancer survivors are primarily risk-based and depend on age at time of diagnosis and treatment, cumulative dosage of both anthracycline and radiation therapy, and additional risk factors associated with cardiac dysfunction [81]. Assessing cardiac function should begin with a detailed history and physical, focusing on cardiac symptoms and risk factors for cardiac disease. Modifiable risk factors for cardiac disease should be addressed, especially obesity, illicit drug use and physical inactivity, and are even more important in this vulnerable population [81].

Imaging techniques are often used to monitor cardiotoxicity during and after chemotherapy. However, serum cardiac biomarkers are increasingly being used. Cardiac troponin T (cTnT) and N-terminal probrain natriuretic peptide (NT-proBNP) concentrations have shown to be effective as markers of early anthracycline-induced cardiotoxicity [63] and have been validated as surrogate markers of late LV structural status among long-term survivors of childhood cancer [26]. In a study of 134 children receiving an anthracycline dose of 300 mg m⁻² for high-risk ALL, elevations in serum cTnT concentrations during the first 90 days of anthracycline treatment were significantly associated with reduced LV end-diastolic posterior wall thickness and LV mass and increased pathologic LV remodelling 4 years later. Similarly, elevations in serum concentrations of NT-proBNP, indicative of cardiomyopathy, during the first 90 days of treatment were correlated with abnormal LV thickness-to-dimension ratios four years after therapy [26]. Thus, as validated surrogate markers of late cardiotoxicity, serum biomarkers of cardiomyopathy (NT-proBNP) and cardiomyocyte injury or death (cTnT) might allow studies to determine whether these markers can be used to tailor anticancer therapy and to determine whether overall outcomes are improved [11].

Imaging studies, such as echocardiography, are also often used during and after chemotherapy because a large percentage of survivors experience reduced LV function and fractional shortening within just a few years after completing therapy [9]. Unfortunately, echocardiography during therapy does not detect early subtle cardiac damage or dysfunction that is associated with late cardiotoxicity in long-term survivors [14, 17]. Additionally, the frequency of screening and the best treatment options if an abnormality occurs are still debated.
Treating anthracycline-induced cardiotoxicity

As the number of survivors of childhood cancer increase, so too will be the number of survivors with adverse effects from cancer therapy. Validated treatments for anthracycline-induced cardiotoxicity remain scarce, and there is no consensus on their use [76]. Once cardiotoxicity occurs, it is often irreversible and progressive (Figure 4) [14]. Among survivors with reduced LV systolic performance, for example, there is often a decreased number of functional cardiomyocytes and stem cells for regenerating cardiac tissue [9]. Drugs often used to treat cardiac disorders, such as heart failure and hypertension, have not been validated in effectively managing anthracycline-induced cardiotoxicity, and have not been found to improve overall morbidity and mortality in this population when used to treat asymptomatic LV dysfunction [14].

Advocating for a heart-healthy lifestyle may be among the most important treatments for these patients [81]. A healthy diet, supervised physical activity tailored to an individual survivor, extracurricular activities, and good mental health are likely to be as important among survivors as they are in the general population to reduce the risk for cardiac dysfunction. Lifestyle counseling and education are especially important among survivors of childhood cancer because of their increased vulnerability to late cardiac effects as adults. However, after addressing conventional risk factor for premature cardiovascular disease, childhood cancer survivors are likely to have additional cancer and cancer therapy-related risk factors for premature cardiovascular disease.

Conclusions

The number of survivors of childhood cancer has grown exponentially and will continue to increase as cancer therapies continue to improve. These patients therefore remain at increased risk of morbidity and mortality from the adverse effects of therapy, especially cardiotoxicity. The need for anthracyclines as a component of treatment for most children, adolescents and young adults with cancer is well recognized. As the number of survivors continues to increase, the need to improve overall morbidity associated with therapy and ultimately their quality of life must also be recognized. An important preventive treatment is the use of dexrazoxane, which can prevent or reduce anthracycline-induced cardiotoxicity as shown in many studies of adults and children with cancer, without decreasing antineoplastic effects or event-free survival. Dexrazoxane should therefore be a concomitant treatment among children, adolescents and young adults treated with anthracyclines now and in the foreseeable future.

Competing Interests

The authors have nothing to disclose and have no conflicts of interest to report.

Supported in part by grants from the National Institutes of Health (HL072705, HL078522, HL053392, CA127642, CA068484, HD052104, AIS0274, CA068484, HD052102, HL087708, HL079233, HL004537, HL087000, HL007188, HL094100, HL095127, HD80002), Chiron, Pfizer Pharmaceuticals, Inc., Lance Armstrong Foundation, Women’s Cancer Association, Roche Diagnostics Corporation, the Scott Howard Fund, the Michael Garil Fund, the Parker Family Foundation, Sofia’s Hope and the American Heart Association.

References

lipshultz SE, lipsitz SR, sallan SE, Dalton VM, mone SM, Gelber.


Herman EH, Ferrans VJ, Myers CE, VanVleet JF. Comparison of the effectiveness of (±)-1,2-Bis(3,5-dioxopiperazinyl-1yl) propane (ICRF-187) and N-acetylcysteine in preventing chronic doxorubicin cardiotoxicity in beagles. Cancer Res 1985; 45: 276–81.


Lipshtult SE, Adams MJ, Colan SD, Constand LS, Herman EH, Hsu DT, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention,
Prevention of cardiotoxicity among survivors of childhood cancer


84 Van Den EC, Caron HN, Dickinson HO, Kremer LC. Cardioprotective interventions for cancer patients receiving anthracyclines. Cochrane Database Syst Rev 2011; 1: CD003917


