CLINICAL PHARMACOLOGY

Anthracycline associated cardiotoxicity in survivors of childhood cancer

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The development of effective antineoplastic therapies for childhood cancer is a great success in modern medicine. Five year survival rates of children diagnosed with cancer in the USA and Western Europe in excess of 70% make long term survivors of childhood cancer a steadily increasing population. Although there is much to celebrate, new challenges lie ahead in treating the systemic sequelae of chemotherapy.[1] Results from the Childhood Cancer Survivor Study (CCSS) showed that 30 years after treatment, the cumulative incidence of chronic health conditions in long term survivors reaches 73%, with a cumulative incidence of 42% for severe, disabling, or life threatening conditions or death.[2] Severe conditions, that are significantly more common in childhood cancer survivors than in their siblings, include: major joint replacement (relative risk (RR) 54.0), congestive heart failure (RR 15.1), second malignant neoplasm (RR 14.8), severe cognitive dysfunction (RR 10.5), coronary artery disease (RR 10.4), cerebrovascular accident (RR 9.3), and renal failure (RR 8.9).[2] Previous CCSS results found that patients who had survived at least 5 years after diagnosis had 10.8-fold increased rates of all cause mortality.[3] The standardised mortality ratio for cardiac causes was 8.2 times higher than expected and the cumulative probability of cardiac death increased 15–25 years after cancer diagnosis. A similar study in a large Nordic cohort documented a standardised mortality ratio of 5.8 for cardiac death and elevated rates of sudden, presumed arrhythmic, deaths.[4]

Chief among adverse late effects is the cardiovascular toxicity of anthracyclines.[5–11] Unfortunately, despite well documented dose related toxicity, the superior disease-free survival rates of regimens including anthracyclines leave limited viable treatment alternatives and the majority of long term paediatric cancer survivors in the Pediatric Oncology Group received an anthracycline during treatment.[12]

NATURAL HISTORY OF ANTHRACYCLINE CARDIOTOXICITY

Mechanism of cardiotoxicity

Several cytotoxic biochemical changes follow anthracycline exposure in cellular studies and animal models, and cardiac dysfunction after in vivo exposure is likely to be the cumulative result of several insults.[9 11 13 14]

A major pathogenic pathway links the generation of radical oxygen species (ROS) and lipid peroxidation of the cell membrane to cardiomyocyte injury acquired during anthracycline exposure. Anthracyclines can induce ROS generation both enzymatically and through the formation of anthracycline–iron complexes.[9 11 13 14] The anthracycline's quinone moiety can be reduced to semiquinone by cytosolic enzymes and then readily donate an electron to oxygen, generating superoxide anions. The superoxide anions can cause subcellular damage directly, or they can be further converted to hydrogen peroxide and the highly reactive hydroxyl radical. These agents are highly toxic and react with lipids, proteins and nucleic acids, resulting in lipid peroxidation, depletion of sulfhydryl-containing peptides, and damage to DNA. Cardiac myocytes have low levels of free radical scavenging systems, such as catalase and glutathione peroxidase, which may sensitise these cells to ROS induced injury.[9 11 13 14]

Cardiolipin is a polyunsaturated, fatty acid-rich phospholipid with a high affinity for anthracyclines found in elevated concentrations in the inner mitochondrial membrane. Anthracyclines are thought to enter mitochondria and to inhibit the respiratory chain by binding to cardiolipin or by interacting with mitochondrial DNA. The high concentrations of cardiolipin within the mitochondria may also increase the susceptibility of cardiac cells to anthracycline damage.[9 11 13 14]

Anthracyclines decrease ATP production by disrupting the cardiac muscle specific gene expression of enzymes critical in energy production, as well as by disrupting structural gene products (for example, cardiac troponins, myosin light chains, and creatine kinase). They may also downregulate mRNA expression for sarcoplasmic reticulum Ca^{2+}-ATPase, which in turn decreases cardiac contractility. Energy depletion reduces the ability of cardiac myocytes to contract effectively and, if severe enough, can lead to cell death. A cycle of interconnected mitochondrial DNA and respiratory chain insults can continue after the end of treatment and in the absence of anthracyclines. These insults may, in part, account for the delayed manifestation of cardiomyopathy.[9 11 13 14]

Table 1 Characteristics of the different types of anthracycline associated cardiotoxicity

Characteristic	Acute cardiotoxicity	Early onset, chronic progressive cardiotoxicity	Late onset, chronic progressive cardiotoxicity
Onset	Within the first week of anthracycline treatment	<1 year after the completion of anthracycline treatment	>1 year after the completion of anthracycline treatment
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

Adapted with permission from Adams MJ, Lipshultz SE. Pathophysiology of anthracycline- and radiation-associated cardiomyopathies: implications for screening and prevention. *Pediatr Blood Cancer* 2005;**44**:600–6. Copyright Wiley-Liss, Inc.[15]

Although the oxidative effects of anthracyclines may not be limited to cardiac cells, rapidly dividing cells may be able to replace those lost to apoptosis or necrosis. Cardiomyocytes—which divide very slowly, if at all—cannot sufficiently replace cells damaged during treatment. Myocardial histology suggests that surviving myocytes compensate to maintain normal cardiac structure via hypertrophy.[5–7] These findings suggest that the characteristically delayed manifestation of symptomatic cardiotoxicity after anthracycline exposure may be related to the eventual failure of a reduced number of unhealthy cardiomyocytes to maintain normal functions.[5–7]

Presentation of disease

The cardiac effects of anthracycline chemotherapy are variable and include asymptomatic electrocardiographic abnormalities, mild hypotension, arrhythmias, myocarditis, pericarditis, acute myocardial infarction, heart failure, and long term cardiomyopathy. Anthracycline induced cardiotoxicity is classified into three categories: (1) acute, (2) early onset chronic progressive, and (3) late onset chronic progressive (table 1). There are some differences in time of onset, clinical characteristics, and associated risk factors.[8–11]

Acute anthracycline cardiotoxicity often presents as a reversible episode of myocardial dysfunction during therapy. The estimated incidence of acute clinically symptomatic toxicity on frontline protocols is less than 1%.[9 12] Within a week of the initial dose, cardiotoxicity manifests as transient clinical symptoms suggesting heart failure. Electrocardiographic abnormalities, including nonspecific ST segment and T wave changes, decreased QRS amplitude, and prolonged QTc interval, are infrequently seen; however, sinus tachycardia is most often present and may represent autonomic dysfunction. Symptoms usually resolve when therapy is discontinued.

Early onset chronic progressive cardiomyopathy occurs within 1 year after anthracycline treatment.[8–12 15] Electrophysiological changes, left ventricular (LV) dysfunction, decreased exercise capacity, and clinical heart failure may develop. Late onset chronic progressive cardiomyopathy occurs more than 1 year after anthracycline treatment.[8–11 15] Cardiac function begins to deteriorate and is associated with myocyte loss, which leads to LV wall thinning and in some cases progressive LV dilation.[5–7] Echocardiographic abnormalities may include decreased LV fractional shortening, end diastolic posterior wall thickness, mass, contractility, and increased LV afterload. Left ventricular dimension may be increased, normal, or decreased. In 115 survivors of childhood acute lymphoblastic leukaemia (ALL), we found that 6 years after anthracycline treatment nearly 65% had abnormal LV structure or function.[5]

Although adults typically develop chronic dilated cardiomyopathy after anthracycline chemotherapy, children at the end of anthracycline treatment have a dilated cardiomyopathy, which may then progress to a restrictive cardiomyopathy.[7] Afterload increases, in spite of normal-to-reduced blood pressure caused by decreased LV wall thickness and mass.[5–7] Thus, the decline in LV function is related more to elevated LV afterload than reduced LV systolic performance.[5–7] Heart failure with preserved LV ejection fraction (LVEF) is increasingly recognised in this exposed population with long term follow-up. In patients without cancer survival rates have remained unchanged over a similar period, whereas in patients with heart failure associated with decreased LVEF, outcomes have improved.[1 11] These findings underscore the need to develop treatments specific to this type of cardiac dysfunction.[10 11 14 16]

EFFECT OF ANTHRACYCLINES ON CHILDREN'S HEARTS

The degree and progression of anthracycline-related toxicity varies widely between individuals, suggesting that genetic predisposition and modifiable and non-modifiable risk factors are present. Several risk factors for cardiotoxicity have been identified (table 2, fig 1). Some risk factors, including cumulative dose, dose rate, dosing schedule, and concomitant treatment, are potentially modifiable.[5–12 15] The accumulation of risk factors leads to a substantial increase in relative risk for early anthracycline cardiotoxicity.[12] Understanding these risk factors will allow clinicians to identify high risk patients and to tailor monitoring and treatment to individual patients.[11]

Table 2 Risk factors for anthracycline cardiotoxicity

Risk factor	Aspects	References
Cumulative anthracycline dose	Cumulative doses >500 mg/m^2 associated with significantly elevated long term risk	Lipshultz *et al* 1991[5]; Krischer *et al* 1997[12]; Lipshultz *et al* 1995[6]; Lipshultz *et al* 2005[7]
Length of post-therapy interval	Incidence of clinically significant cardiotoxicity increases progressively post-therapy	Lipshultz *et al* 1991[5]; Lipshultz *et al* 1995[6]; Lipshultz *et al* 2005[7]
Rate of anthracycline administration	Prolonged administration to minimise circulating dose volume may decrease toxicity; results are mixed	Lipshultz *et al* 2002[23]
Individual anthracycline dose	Higher individual anthracycline doses are associated with increased late cardiotoxicity, even when cumulative doses are limited	Lipshultz *et al* 1995[6]; Lipshultz *et al* 2005[7]
Type of anthracycline	Liposomal encapsulated preparations may reduce cardiotoxicity. Conflicting data exist about anthracycline analogues and cardiotoxicity differences	Wouters *et al* 2005[14]; Barry *et al* 2007[11]; Van Dalen *et al* 2006[20]
Radiation therapy	Cumulative radiation dose >30 Gy; prior or concomitant anthracycline treatment	Giantris *et al* 1998[9]; Adams *et al* 2005[15]
Concomitant therapy	Trastuzumab, cyclophosphamide, bleomycin, vincristine, amsacrine, and mitoxantrone may increase susceptibility/ toxicity. Others are implicated as well	Giantris *et al* 1998[9]; Barry *et al* 2007[11]
Pre-existing cardiac risk factors	Hypertension; ischaemic, myocardial, and valvular heart disease; prior cardiotoxic treatment	Barry *et al* 2007[11]
Comorbidities	Diabetes, obesity, renal dysfunction, pulmonary disease, endocrinopathies, electrolyte and metabolic abnormalities, sepsis, infection, pregnancy	Barry *et al* 2007[11]
Age	Both young and advanced age at treatment are associated with elevated risk	Lipshultz *et al* 1991[5]; Lipshultz *et al* 1995[6]
Sex	Females are at greater risk than males	Lipshultz *et al* 1995[6]
Additional factors	Trisomy 21; African American ancestry	Krischer *et al* 1997[12]

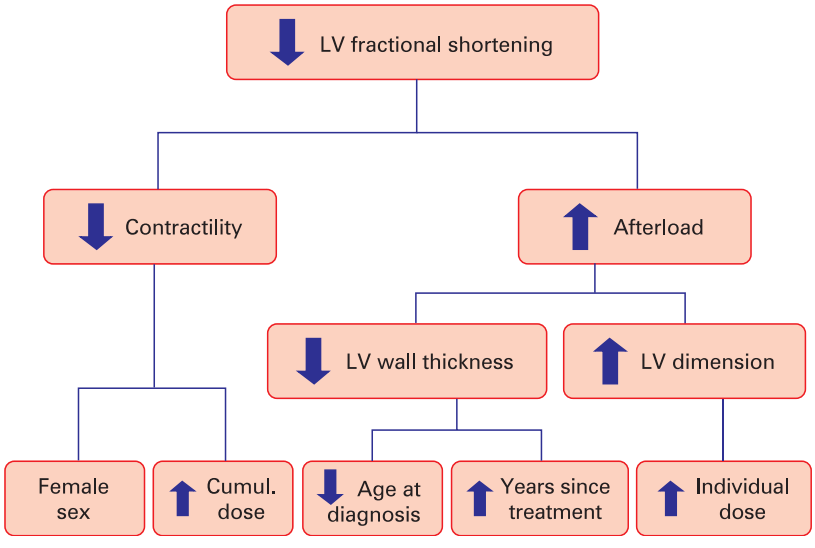

Figure 1 Demographic and clinical characteristics associated with cardiac and non-cardiac findings in long term survivors of childhood cancer treated with anthracycline therapy. Summary of significant associations of multivariable analyses of risk of reduced left ventricular fractional shortening 8 years after anthracycline (doxorubicin) treatment for childhood acute lymphoblastic leukaemia or osteosarcoma.[6] Reproduced with permission from Wouters KA, Kremer LCM, Miller TL, *et al*. Protecting against anthracycline-induced myocardial damage: a review of the most promising strategies. *Br J Haematol* 2005;**131**:561–78. Copyright© Blackwell Publishing 2005.[14]

Non-modifiable cardiotoxicity risk factors

Age at treatment

Patients treated at a younger age appear to be more vulnerable to anthracycline induced cardiotoxicity.[5–7 9] We found that treatment before age 4 years was a significant risk factor for later cardiac dysfunction.[7]

Length of follow-up

The importance of continuing to follow children with, or at risk for, premature symptomatic cardiovascular disease cannot be overemphasised. With longer follow up after anthracycline treatment, the prevalence and severity of cardiac abnormalities increase.[5–7] This increase may relate to the emergence of new cases of late onset cardiac toxicity and to the worsening of previously detected early onset chronic progressive cardiomyopathy.

In children with ALL, LV contractility is substantially depressed immediately after doxorubicin treatment (negative Z score) but returns to normal over the next 6 years.[7] From 6 to 14 years later, however, LV contractility declines notably (fig 2). Thus, the importance of lifetime follow-up cannot be overstated and preventing late cardiotoxicity must be a research priority,[7 17] particularly as the number of asymptomatic cancer survivors at risk for cardiac dysfunction later in life increases. More than 6 years of follow-up is necessary to identify those long term survivors at risk for cardiac dysfunction.[7]

Sex

Girls are at significantly greater risk than boys for late depressed contractility, even when receiving the same cumulative dose of doxorubicin.[6 7] Though the underlying cause of this difference is not yet known, differences in sex specific body fat percentage may be involved.[6]

Genetic factors

High inter-patient variability in development and progression of cardiac toxicity after anthracycline use suggests that genetic factors (natural genotypes or induced changes) may affect anthracycline processing and eventual toxic effects.[11] Mutations effecting iron metabolism are particularly implicated. Mice with hereditary haemochromatosis, a genetic disorder involving excess iron uptake and storage, are significantly more sensitive to the cardiotoxic effects of anthracyclines, than are wild type mice. Anthracycline associated cardiac mitochondrial DNA (mtDNA) mutations have also been implicated in susceptibility to cardiotoxicity.[11] Whether these mutations are inherent or induced is not yet known.

Modifiable cardiovascular risk factors

The long term risk of anthracycline exposure can be reduced by modifying risk factors that minimise initial cardiac damage.

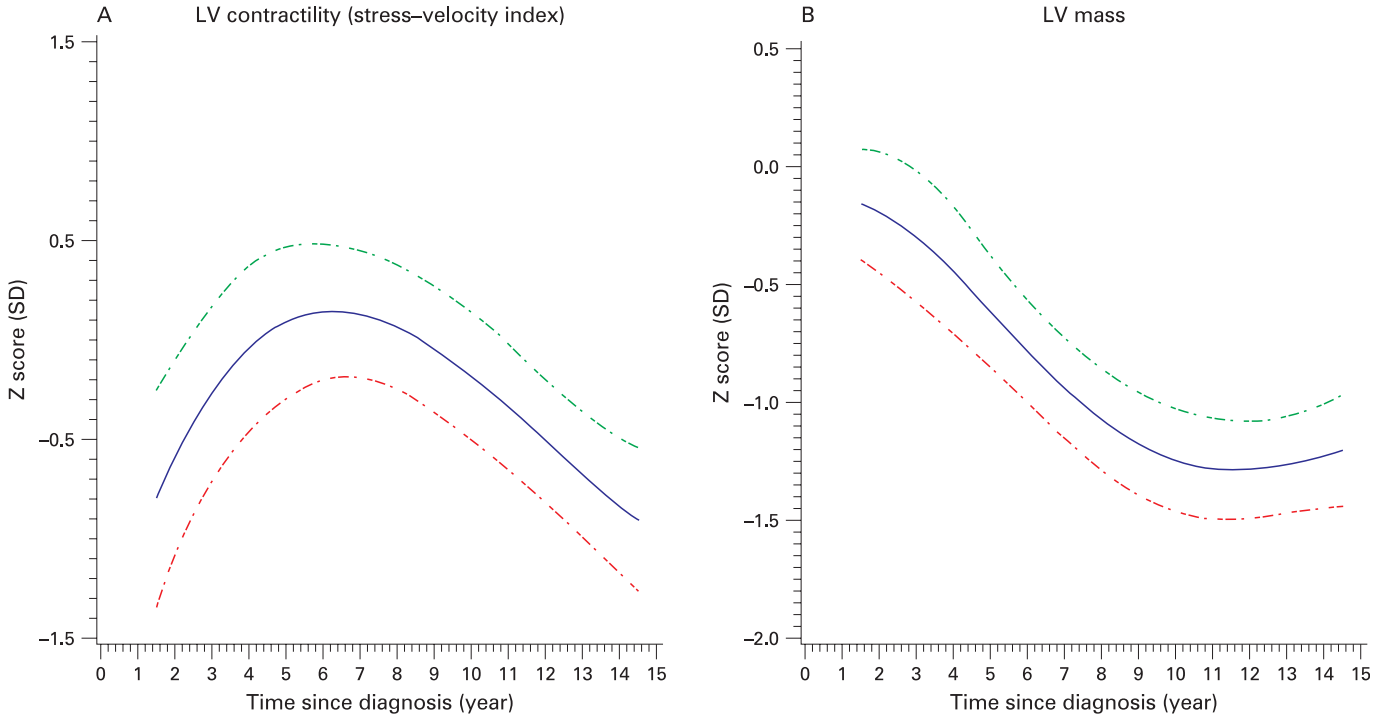

Figure 2 Z scores of left ventricular contractility (panel A) and left ventricular mass (panel B) from 115 long term survivors of acute lymphoblastic leukaemia treated with doxorubicin, by time since diagnosis. A model of follow-up data for all children is given. The solid line is the overall group mean. A Z score of zero indicates the normal population mean. The dashed lines are the upper and lower 95th centile confidence bounds from the predicted mean. Reproduced from Lipshultz SE, Lipsitz SR, Sallan SE, *et al*. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *J Clin Oncol* 2005;**23**:2629–36. Reprinted with permission from the American Society of Clinical Oncology.[7]

Cumulative dose

A high cumulative anthracycline dose is a well recognised risk factor for cardiac damage and remains the best predictor of eventual cardiac dysfunction, including increased afterload and decreased contractility.[5–11 14 18–20] The risk of cardiotoxicity with 550 mg/m^2 or more is five times higher than that of lower cumulative doses.[12] A cumulative doxorubicin dose above 300 mg/m^2 is a significant risk factor for decreased cardiac function 8 years after therapy.[21] However, there is no absolutely safe dose of anthracycline; even the lowest clinically relevant doses can cause subsequent cardiac dysfunction.[7]

Although lowering cumulative dose might appear to be a straightforward solution to reducing cardiotoxicity, cardioprotection must be balanced with oncologic efficacy.[7 16 22] Fortunately, the ratio of increasing cumulative dose to increasing treatment efficacy begins to plateau at higher doses and the greatest gains in antineoplastic activity occur within a range of slowly increasing cardiac risk.[16 22] In this case, the optimal cumulative anthracycline dose is determined by taking both competing risks into account.

Rate of administration

Peak serum concentrations of anthracyclines can be controlled in part by altering the rate of doxorubicin administration. Prolonged infusion therapy has been recommended to reduce anthracycline cardiotoxicity.[10 11 14 16 18–20 23 24] This practice became standard before confirmation by randomised trials and subsequent studies have questioned its efficacy to reduce long term cardiotoxicity. Our blinded, randomised trial in children with newly diagnosed ALL comparing bolus administration of doxorubicin given over <1 h to 48 h infusion for each of 12 dosages found no significant benefit.[23] After a median 1.5 years of follow-up, multiple echocardiographic measurements showed abnormalities in both groups, including a significant decrease in median LV fractional shortening (LVFS) and LV contractility, and a significant increase in LV peak systolic wall stress. In children with ALL randomly assigned to receive anthracyclines by bolus or by 6 h continuous infusion after subclinical abnormal cardiac function, continuous infusion did not significantly reduce toxicity.[24] Furthermore, prolonged infusions require additional hospitalisation and costs, possibly increase morbidity, and may create additional stress to patients and families.[23]

Concomitant radiation and other chemotherapy agents

Radiation therapy (RT) is frequently combined with chemotherapy in children with cancer. Radiation may worsen the cardiotoxic effects of anthracyclines, but whether this effect is additive or synergistic is unclear.[1 8–11 14 15] Other antineoplastic drugs, including mitoxantrone, high dose cyclophosphamide, amsacrine, bleomycin, vincristine and trastuzumab, may also augment doxorubicin cardiotoxicity.[1 8–12 14 15 18–20]

Heart 2008;**94**:525–533. doi:10.1136/hrt.2007.136093

CURRENT MONITORING, PREVENTIVE, AND TREATMENT PRACTICES

Monitoring cardiac function may be useful during and after anthracycline treatment.[1 8–12 14 15 22 25] Without evidence based guidelines for monitoring of cardiac function during treatment, monitoring schedules and methods vary widely in both protocol and practice.[1 8–12 14 15 22 25] For children receiving cardiotoxic treatment, the American Heart Association's class I recommendation is serial monitoring by echocardiography, including Doppler analysis, M mode echocardiography, two dimensional transthoracic echocardiography, and, when indicated, transoesophageal echocardiography, at baseline and with recurrent re-evaluations.[11] Suggested guidelines for stopping anthracycline treatment are neither codified nor sufficient.[1 8–12 14 15 22 25]

Serological evaluation of cardiac function may also be useful during treatment, although the relationship between short term changes and late cardiotoxicity remains to be determined.[1 10 11 13 14 15 26 27] Elevated serum cardiac troponins—proteins mostly of the cardiac myocyte sarcomere released after cellular damage—appear to be directly related to the degree of cardiac damage when clearance is normal.[1 10 11 13–15 26 27] N-terminal pro B type natriuretic peptide (NT-proBNP), a biomarker of unhealthy heart muscle, and high sensitivity C reactive protein (HsCRP), a marker of generalised inflammation, may also help to assess cardiac status during and after treatment in children with cancer.[11] NT-proBNP is an independent predictor of cardiovascular events and mortality in populations with chronic heart failure (CHF), acute coronary syndromes, prior myocardial infarction, vascular disease, elevated coronary risk, and in community based samples. Preliminary results suggest that NT-proBNP may also help to identify cardiac stress before irreversible damage in children receiving anthracyclines.[11] HsCRP is also an independent predictor of outcome in some studies of adults with ischaemic and non-ischaemic cardiomyopathy and may be an important indicator of overall cardiovascular health during and after treatment.[11]

Table 3 Strategies evaluated for cardioprotective potential in the presence of anthracyclines

Class	Example
Antihistamines	Chlorpheniramine
	Ketotifen
	Disodium cromoglycate
Antioxidants	N acetyl cysteine
	α tocopherol
	Carvedilol
	Coenzyme Q10
	Resveratrol
Chelating agents	Dexrazoxane
Cytokines	Erythropoietin
	Granulocyte stimulating factor
	Thrombopoietin
Energy regulators	Adenosine
	Carnitine
Enzyme inhibitors	COX 2 inhibitors
	Digoxin
	Amrinone
Exercise	
Hormones	Oestrogen
Inhibitors of mediator release	Cromolyn
Ion regulators	Calcium channel blockers
	α and β adrenergic antagonists
Membrane stabilisers	Steroids
	Taurine
Metabolic agents	Probucol
	Lovastatin
Miscellaneous agents	Bismuth
	Zinc
	Cadmium
Uptake inhibitors	Tetracyclines

COX, cyclo-oxygenase.
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Preventing cardiotoxicity and cardiovascular disease

Although the symptomatic treatment of cardiovascular disease in childhood cancer survivors is important, available treatments can often only delay the progression of cardiac dysfunction.[16 28 29] The most effective way to reduce late cardiotoxicity is to prevent initial damage[16 26 27] (see also recent reviews).[1 10 11 14 18]

Cardioprotectants: the case for dexrazoxane

The primary way to attenuate cardiotoxicity is during anthracycline exposure. Several compounds have been tested for their ability to reduce cardiovascular toxicity, specifically by controlling free radical oxidative stress (table 3).[8 13 14 18–20 26 27] Most have had only limited success.

Currently, the most promising cardioprotectant for use in children is dexrazoxane.[8 13 14 18–20 26 27] A member of the bisdioxopiperazine family similar to ethylene diamine tetra-acetic acid (EDTA), it chelates intracellular iron. Dexrazoxane scavenges free iron as well as transferrin and ferritin bound iron, thereby inhibiting the formation of the anthracycline–iron complexes responsible for generating myocardiocyte damaging ROS.[8 13 14 18–20 26 27] The reduction in cardiotoxicity from high doses of doxorubicin by dexrazoxane has been reviewed.[1 10 11 14 15 18 19 26 27]

Dexrazoxane was approved in 2002 by the US Food and Drug Administration for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who had received a cumulative doxorubicin dose of at least 300 mg/m^2 and would continue to receive anthracycline treatment to maintain tumour control.[11] Dexrazoxane is currently recommended by the American Society of Clinical Oncology for this indication.[25]

Clinical trials with dexrazoxane in children have been encouraging. In a randomised trial of children diagnosed with ALL treated at the Dana Farber Cancer Institute ALL Consortium, children who

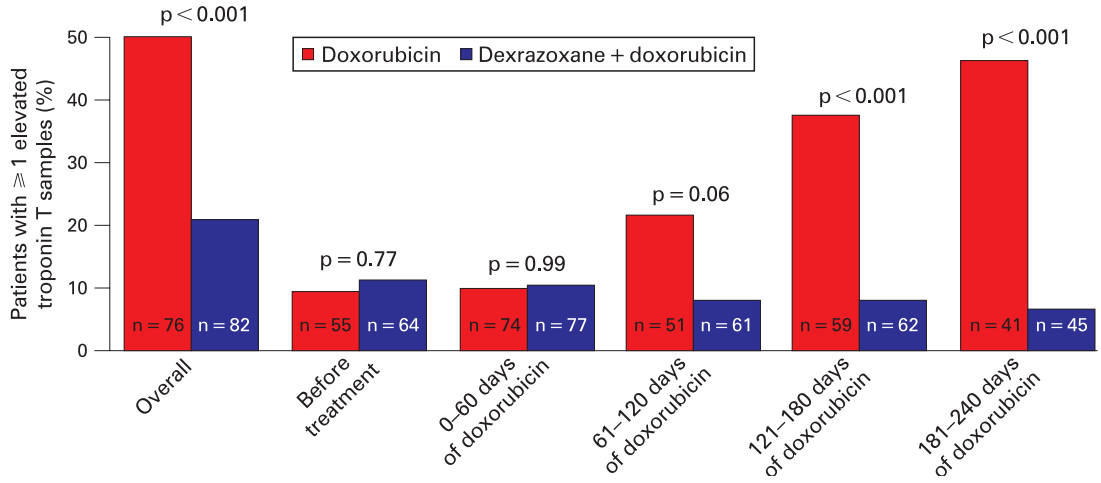

Figure 3 Percentage of patients with at least one elevated serum cardiac troponin T level overall, before and during treatment with doxorubicin. An elevated level of serum cardiac troponin T was defined as one that exceeded 0.01 ng/ml. The number of patients in whom serum cardiac troponin T was measured at least once during the specified intervals is shown in each bar. Reproduced with permission from Lipshultz SE, Rifai N, Dalton VM, *et al*. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med* 2004;**351**:145–53. Copyright© 2004, Massachusetts Medical Society. All rights reserved.[27]

received dexrazoxane before doxorubicin were significantly less likely to have cardiac injury during treatment as measured by elevated serum levels of cardiac troponin T (cTnT) (fig 3).[13 26 27]

Dexrazoxane is the only proven cardioprotectant in cancer patients receiving anthracycline chemotherapy.[10 11 14 18 19] Although dexrazoxane may decrease the antineoplastic activity of doxorubicin, no convincing evidence shows that it impairs survival after doxorubicin treatment or that it has any new or clinically relevant sequelae (infection, haemorrhage, deaths, or necessity for change of dosage).[10 11 14 18 19] Of 16 clinical trials performed in seven countries over the past 10 years involving more than 1500 patients, only one reported that dexrazoxane lowered the response rate, but it did not affect survival.[10 11 14 18 19] Thus, where evidence shows that it may be beneficial, dexrazoxane has been recommended for use in paediatric research protocols to evaluate the long term balance of cardioprotection and the possible effect on antitumour efficacy.[10 11 14 18 19]

Pharmacologic options for treating anthracycline associated cardiotoxicity

Treating of anthracycline induced heart disease in childhood cancer survivors is of critical clinical importance.

Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme (ACE) inhibitors reduce LV afterload and tend to slow the progression of LV dysfunction. Thus, they may be useful in treating long term cancer survivors who often develop symptomatic LV dysfunction. The success of ACE inhibitors in adults[11 14] led to their evaluation in children.[19] In a study of the long term effect of ACE inhibitors in childhood cancer survivors with anthracycline induced cardiac dysfunction, enalapril initially significantly improved LV dimension, afterload, fractional shortening, and mass.[19] However, these gains were lost after 6–10 years on enalapril. Furthermore, LV wall thickness deteriorated throughout the study, as did LV contractility and systolic blood pressure. After 6 years of treatment, all patients who had started with CHF had progressed to cardiac transplantation or cardiac death. Although ACE inhibitors did not prevent progression of LV dysfunction and thinning of LV walls, they did provide some respite in the form of afterload reduction.

Growth hormone therapy

Growth hormone (GH) may act indirectly on the heart through the action of insulin-like growth factor 1 (IGF-1) to maintain adequate LV mass.[29] For survivors of childhood cancer, GH deficiency is a common problem.[29] When GH is insufficient, thin LV walls and decreased LV contractility are believed to lead to increased LV afterload and LV dysfunction. Growth hormone deficiency also increases cardiac related mortality and dyslipidaemia.[29] Although small pilot studies in adults with impaired LV structure and function found improved cardiac function and exercise performance, as well as an increased cardiac mass after GH therapy, several randomised trials have found no clinical benefits of GH treatment, despite the increase in LV mass.[29]

In anthracycline treated survivors of childhood cancer with reduced LV wall thickness and function, GH therapy temporarily improved wall thickness.[29] This improvement was lost after treatment was discontinued.[29] A similar group of untreated controls showed no changes in wall thickness. Growth hormone therapy did not affect progressive LV dysfunction.[29]

Secondary prevention: the heart healthy life

For childhood cancer survivors unable to benefit from cardioprotective strategies during

Anthracycline associated cardiotoxicity: key points

- Cardiotoxicity is a primary limiting factor in the use of anthracycline chemotherapy.
- Late cardiotoxicity in children and young adults may be related to acute damage during treatment.
- The potentially long latency and high cumulative incidence of chronic cardiac dysfunction related to cancer treatment indicates that long term monitoring of asymptomatic individuals is essential.
- Risk factors have helped identify patients at high risk for late cardiomyopathy and heart failure.
- Lifestyle changes may reduce long term risk.

chemotherapy who sustained cardiotoxicity, secondary prevention of cardiac disease should not be dismissed. All patients should be educated about the cardiotoxic risks of their treatments and about the need for lifelong monitoring of heart function and coronary artery disease risks.[1 10 11 14 15 17 25 30] Integral to education is a concerted effort to making heart healthy decisions.

Diet, obesity, and drugs

A heart healthy diet low in saturated fat is recommended for these patients, and salt intake should be restricted to 2.5 g/day. However, scientific evidence on the effects of a modified diet and lifestyle in patients exposed to anthracyclines is limited.[10]

Ideal body weight should be maintained. Obesity is associated with increased cardiovascular morbidity and mortality and is a major preventable coronary risk factor. Its prevalence is increased in survivors of childhood cancer, especially in those with ALL. Other risk factors for preventing cardiovascular disease should be minimised in these patients, who are at increased risk for premature symptomatic cardiovascular disease. These risk factors include diabetes, hypertension, and endocrinopathies. These patients should also be considered higher risk during anaesthesia, pregnancy, severe infections, or other conditions of cardiovascular stress. The impact of obesity on anthracycline induced cardiomyopathy is not known.

Alcohol consumption, illicit drug use—especially cocaine or other stimulants—and cigarette smoking should be discouraged in patients at risk for cardiomyopathy, especially in patients with LV dysfunction, because these habits may further impair LV function.[25]

Exercise

Aerobic exercise can be beneficial, but patients should undergo maximal or submaximal exercise testing to ensure that they have stable cardiovascular function before exercise programmes are recommended. Isotonic exercise, such as weight lifting, should be pursued only under the direct supervision of a cardiologist and exercise physiologist.[10 30]

Concomitant trastuzumab treatment increases susceptibility to anthracycline cardiotoxicity.[11 14] Neuregulin, a ligand for the erbB4/erbB2 receptor complex targeted by trastuzumab, may be important in cardioprotection.[11] In rats, exercise training before combination chemotherapy appears to be cardioprotective through endogenous upregulation of neuregulin or other cardioselective signalling pathways.[11] Clinical studies have not yet investigated this claim.

One pilot study that examined exercise in children with chronic illnesses included two paediatric cancer survivors treated with anthracyclines.[30] Both had substantially depressed LV function and were treated in a paediatric cardiac rehabilitation centre with a 12 week, hospital based physical activity programme.[30] The intervention notably reduced their body fat and improved their strength. Other risk factors for premature cardiovascular disease also improved.[30]

The importance of assessing the impact of an intervention on total cardiac risk, not just risk for heart failure, is also illustrated in the above study.[10 11 30] Improvement was sustained for at least 1 year.[30] However, in one child, although LV contractility improved, LV afterload increased, leading to a more dilated and thinner LV.[30] The overall effects of exercise may be highly beneficial in some survivors, but harmful in others, making close monitoring of these patients imperative when using exercise as a therapeutic modality.[30]

CONCLUSION

Anthracycline chemotherapy can lead to a broad range of cardiovascular abnormalities, many of which are progressive and of late onset. Although more children will continue to benefit from

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anthracyclines and become cancer survivors, it is clear that there is no "safe dose" free from potential cardiovascular damage. Cumulative dose and length of follow-up after anthracycline exposure both effect the development of late cardiotoxicity; in group analyses, cardiotoxicity in long term survivors is progressive regardless of dose.[5–7 11] Survivors should be counselled about the presence of cardiac risk, encouraged to follow a preventive heart healthy lifestyle, and monitored lifelong with appropriate tests to identify subclinical cardiovascular disease. With regard to preserving cardiac function without compromising anti-tumour efficacy, recent clinical data from paediatric and adult oncology trials support the use of dexrazoxane during treatment on research protocols. With the increased success of paediatric cancer treatment, cardiac care providers must assume their role in the prevention, diagnosis, and management of treatment related cardiovascular disease.

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