Cardiology in the Young (2015), **25(Suppl. 2)**, 107–116
doi:10.1017/S1047951115000906

Original Article

Cardiac complications in childhood cancer survivors treated with anthracyclines*

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Abstract Cardiovascular complications are among the leading causes of morbidity and mortality among survivors of childhood cancer, after cancer relapse and secondary malignancies. Although advances in cancer treatment have improved the 5-year survival rates, the same treatments, such as anthracyclines, that cure cancer also increase the risk for adverse cardiovascular effects. Anthracycline-related cardiotoxicity in survivors of childhood cancer is progressive and can take years to develop, initially presenting as sub-clinical cardiac abnormalities that, if left undetected or untreated, can lead to heart failure, myocardial infarction, or other clinical cardiac dysfunction. A higher cumulative dose of anthracycline is associated with cardiotoxicity in children; however, sub-clinical cardiac abnormalities are evident at lower doses with longer follow-up, suggesting that there is no "safe" dose of anthracycline. Other risk factors include female sex, younger age at diagnosis, black race, trisomy 21, longer time since treatment, and the presence of pre-existing cardiovascular disease and co-morbidities. Cardioprotective strategies during treatment are limited in children. Enalapril provides only temporary cardioprotection, whereas continuous anthracycline infusion extends none. On the other hand, dexrazoxane successfully prevents or reduces anthracycline-related cardiotoxicity in children with cancer, without increased risks for recurrence of primary or second malignancies or reductions in anti-tumour efficacy. With more childhood cancer survivors now reaching adulthood, it is vital to understand the adverse effects of cancer treatment on the cardiovascular system and their long-term consequences to identify and establish optimal prevention and management strategies that balance oncologic efficacy with long-term safety.

Keywords: Anthracyclines; cardiotoxicity; childhood cancer survivors; dexrazoxane

Received: 5 February 2015; Accepted: 1 May 2015

Cardiovascular complications are among the leading causes of morbidity and mortality among survivors of childhood cancer, after cancer relapse and secondary malignancies.[1,2] Advances in cancer treatment have improved the 5-year survival rates over the past 3 decades for children diagnosed with cancer, from about 60 to more than 80%;[3] however, the same treatments that cure cancer also increase the risk of adverse effects in cardiovascular and other organ systems.

Clinical and sub-clinical cardiovascular damage, heart failure, coronary artery disease, and cerebrovascular events are examples of some treatment-related health complications in survivors of childhood cancer.[2,4,5] Compared with siblings, survivors have an almost six-fold increased risk for heart failure, a five-fold increased risk for myocardial infarction, a six-fold increased risk for pericardial disease, and an almost five-fold increased risk for valvular abnormalities (Table 1).[6] Furthermore, beyond the age of 35 years, survivors have an almost 11-fold increased

*Presented at Johns Hopkins All Children's Heart Institute, International Pediatric Heart Failure Summit, Saint Petersburg, Florida, United States of America, 4–5 February, 2015.

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Table 1. HRs and 95% CIs of reported cardiac conditions in childhood cancer survivors compared with the sibling control group.*

	Congestive heart failure		Myocardial infarction		Pericardial disease		Valvular abnormalities	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
All diagnoses	5.9 (3.4–9.6)	<0.001	5.0 (2.3–10.4)	<0.001	6.3 (3.3–11.9)	<0.001	4.8 (3.0–7.6)	<0.001
Leukaemia	4.2 (2.3–7.4)	<0.001	3.3 (1.2–8.6)	0.018	2.6 (1.2–5.5)	0.012	2.6 (1.3–4.9)	0.004
Brain tumour	2.2 (1.0–4.7)	0.039	6.1 (2.3–16.2)	<0.001	2.9 (1.2–6.8)	0.014	2.2 (1.0–4.9)	0.052**
Hodgkin's lymphoma	6.8 (3.9–11.7)	<0.001	12.2 (5.2–28.2)	<0.001	10.4 (5.4–19.9)	<0.001	10.5 (6.1–17.9)	<0.001
Non-Hodgkin's lymphoma	5.1 (2.6–10.0)	<0.001	2.9 (0.9–9.6)	0.085	4.7 (2.1–10.7)	<0.001	5.4 (2.7–10.8)	<0.001
Kidney tumour	4.9 (2.4–10.0)	<0.001	***	–	2.4 (0.8–6.9)	0.12**	3.6 (1.6–8.4)	0.003
Neuroblastoma	4.1 (1.7–9.7)	0.002	11.1 (3.3–36.9)	<0.001	5.1 (1.9–14.0)	0.002	7.7 (3.6–16.5)	<0.001
Sarcoma	4.6 (2.4–8.8)	<0.001	3.6 (1.2–11.0)	0.026	5.1 (2.4–11.0)	<0.001	2.2 (1.0–4.9)	0.050**
Bone cancer	6.5 (3.6–12.0)	<0.001	4.2 (1.5–11.8)	0.007	4.9 (2.3–10.5)	<0.001	4.4 (2.3–8.5)	<0.001

CI = confidence interval; HR = hazard ratio

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*Adjusted for gender, race, household income, education, and tobacco use

**Not significant at p = 0.05

***Unable to estimate

risk for heart failure, compared with siblings, indicating that risks are persistent and progressive over the years.[7] Overall, about 65% of anthracycline-treated childhood cancer survivors will have some kind of late cardiovascular abnormality.[8]

Mechanisms of athracycline-induced cardiotoxicity

Anthracyclines, a commonly used class of chemotherapeutic agents, impose substantial risk of cardiotoxicity through several possible mechanisms.[9] The most commonly accepted is the oxidative stress hypothesis, which suggests that generating reactive oxygen species and lipid peroxidation of the cell membrane damage cardiomyocytes.[10] In addition, a recent report suggests that alterations in topoisomerase II β by anthracyclines may also be important in cardiac injury.[11] Understanding the mechanism of injury may help develop targeted strategies for the prevention and treatment specific to anthracycline-induced cardiac injury.

Course of cardiotoxicity

Cardiotoxicity in survivors of childhood cancer is progressive and can take years to develop (Fig 1).[12] The first evidence of anthracycline-induced cardiotoxicity is sub-acute cardiac damage that manifests as depressed myocardial contractility and, if left undetected or untreated, can progress to heart failure during or shortly after completion of therapy.[13] In a previous study of patients with a diagnosis of acute lymphoblastic leukaemia, acute heart failure – heart failure beginning within 1 year of completion of doxorubicin therapy – was identified in 10% (11/115) of those treated with anthracyclines during childhood. All 11 patients improved with anti-congestive therapy.[8] Between 3 and 10 years later, subsequent recurrence of heart failure was seen in five of these patients, two of whom underwent heart transplantation.[8] Those patients who initially presented with early sub-clinical cardiac abnormalities had a dilated-type cardiomyopathy, which was characterised by reduced left ventricular fractional shortening and left ventricular contractility along with left ventricular dilation; however, over time, the cardiac abnormalities became more of a restrictive-type cardiomyopathy, with normal-to-reduced left ventricular dimensions and markedly reduced left ventricular wall thickness for body surface area, reduced left ventricular fractional shortening, and reduced left ventricular contractility (Fig 2).[8]

In 115 survivors, after a median follow-up of 17 years, left ventricular dimension for body surface area decreased with a subsequent rise in left ventricular wall thickness for body surface area, resulting in a normal left ventricular thickness-to-dimension ratio, a marker of left ventricular re-modelling, and reduced left ventricular mass. This type of chronic cardiomyopathy is marked by a shrinking myocardial and cavity size ("Grinch" syndrome) for body surface area, and it may progress to heart failure, heart transplantation, or death in childhood cancer survivors.[12,14,15]

Risk factors for cardiotoxicity

Risk factors associated with cardiotoxicity include higher cumulative anthracycline dose, female sex, younger age at diagnosis, black race, trisomy 21, longer time since treatment, and the presence

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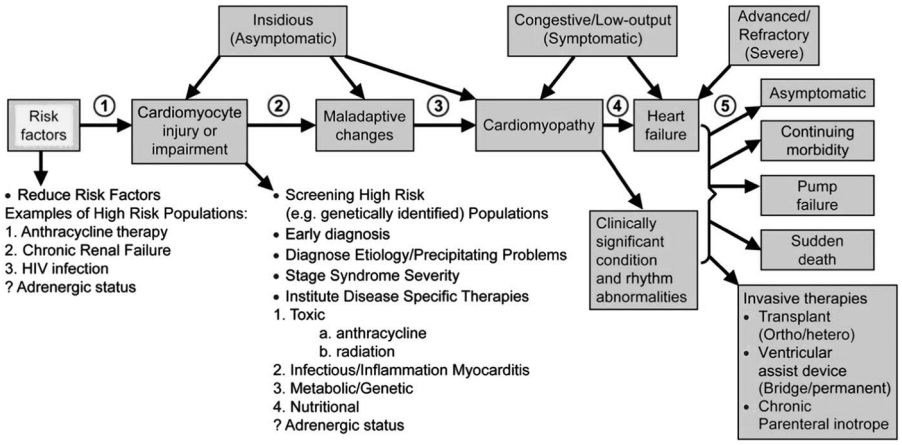

Figure 1.
Stages in the course of paediatric ventricular dysfunction. Preventive strategies progressively become less effective as the number increases. For example, primary prevention is possible at number 1; secondary prevention is possible at numbers 2, 3, and 4. Treatment strategies have a greater impact with higher numbers but longer effects with lower numbers. For example, treatment is possible at numbers 4 and 5 to reduce sequelae. Biomarkers/surrogate end points are potentially more useful with lower numbers for possible alteration of course with interventions and are potentially more useful with higher numbers for decisions about transplantation (Reprinted with permission from Elsevier[15]).

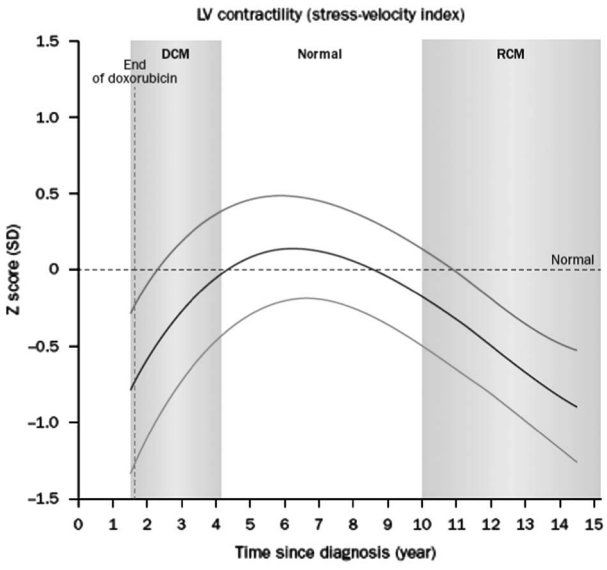

Figure 2.
Progressive cardiac dysfunction after doxorubicin therapy in children treated for acute lymphoblastic leukaemia. DCM was characterised by echocardiographic signs of reduced LV fractional shortening and contractility with LV dilation. In time, the pattern changed, and children showed signs consistent with a RCM: normal to reduced LV dimension with significantly reduced LV thickness, fractional shortening, and contractility. The blue line indicates the overall group mean in this model. Green and red lines are the upper and lower 95% CI from the predicted mean (Reprinted with permission from the American Society of Clinical Oncology[12]). CI = confidence interval; DCM = dilated cardiomyopathy; LV = left ventricle; RCM = restrictive cardiomyopathy.

of pre-existing cardiovascular disease and co-morbidities.[16] In a recent study of documented, symptomatic cardiac events, a higher cumulative anthracycline dose was associated with a higher risk for cardiac events in survivors of childhood cancer.[17] The risk of cardiotoxicity is 11 times higher in children who receive cumulative anthracycline doses of $>300\ mg/m^2$ compared with those who receive lesser dosages;[18] however, sub-clinical cardiac abnormalities are evident at lower doses,[19,20] suggesting that there is no "safe" dose of anthracycline.[21] A particular study specifically designed to evaluate the effects of very low doses of anthracyclines ($\leqslant 100\ mg/m^2$) on left ventricular function in 91 survivors of childhood cancer found, after a mean of 9.8 years from diagnosis, that 28% had abnormal left ventricular posterior wall thickness ($\geqslant 2$ SD) and four patients had an abnormal left ventricular fractional shortening (<28%).[20]

Female childhood cancer survivors had a greater reduction in left ventricular contractility and lower left ventricular mass compared with males after a median follow-up of 8.1 years, even after receiving the same cumulative dose of doxorubicin. In addition, higher cumulative dose was associated with an even greater reduction in contractility for females, further broadening the gap between sexes (Fig 3).[22] Girls tend to have more body fat than boys; therefore, this risk might be partially explained by the low clearance of anthracyclines with increased body fat and its longer persistence in higher concentrations in non-adipose tissues, including the heart.[22] Younger age at diagnosis, particularly before 4 years of age, is a risk factor for anthracycline cardiotoxicity.[22] Damage induced by anthracyclines could impair the heart's ability to grow in these young patients, increasing their vulnerability for cardiac dysfunction.

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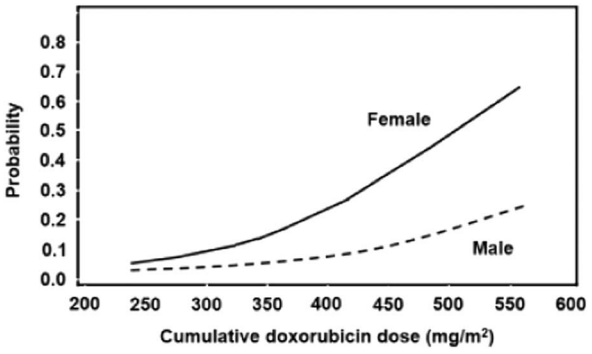

Figure 3.
Probability of depressed contractility as a function of the cumulative dose of doxorubicin in female and male patients (Reprinted with permission from the Massachusetts Medical Society[22]).

Historically, cranial irradiation has been the standard treatment for childhood leukaemia and brain cancers and to prevent brain metastases. Unlike chest-directed radiation, cranial radiation increases the risk of cardiotoxicity more indirectly. Cancer survivors exposed to cranial radiation, compared with those unexposed, had decreased left ventricular mass and left ventricular dimensions over a 10-year follow-up period.[23] These changes in cardiac structure were associated with reduced concentrations of insulin-like growth factor-1 that were likely related to growth hormone deficiency.[23]

The presence of traditional cardiovascular risk factors further increase the risk of cardiovascular disease in childhood cancer survivors treated with cardiotoxic treatments. An analysis of 5-year survivors from the Childhood Cancer Survivor Study reported on 10,724 survivors followed-up longitudinally for the development of traditional cardiovascular risk factors.[5] The cumulative prevalence of all cardiovascular risk factors, except obesity, increased with age in survivors and was greater in survivors than in siblings. Furthermore, the cumulative incidence of all major cardiac events was greater in survivors than in siblings and was also associated with exposure to cardiotoxic therapies. In a related study, a higher number of traditional cardiovascular risk factors was associated with a higher cumulative incidence of cardiovascular disease, such that the cumulative incidence for having two or more risk factors is almost three times as high as having none. Furthermore, the cumulative incidence is even higher when the risk factors are coupled with exposures to cardiotoxic treatments.[24]

It is important to highlight that cardiovascular risk factors can develop in survivors both exposed and unexposed to cardiotoxic therapies.[25] Compared with siblings, in both exposed and unexposed survivors, the increase in cardiovascular abnormalities results from abnormal left ventricular structure and function, an increase in traditional risk factors for atherosclerotic disease – for example, elevated body mass index, insulin level, and non-high density lipoprotein cholesterol – and systemic inflammation.[25] These results support the need for comprehensively assessing the global risk for cardiovascular disease in all childhood cancer survivors.

Cardioprotection during cancer treatment

Dexrazoxane is an iron chelator that reduces the formation of anthracycline–iron complexes, thus reducing the generation of reactive oxygen species.[26,27] It also mitigates doxorubicin-induced DNA damage by hindering the action of topoisomerase 2-β.[11,28] Earlier pre-clinical studies have found evidence of cardioprotection from dexrazoxane, which prompted its exploration in humans.[29] At present, dexrazoxane is the only drug approved to reduce doxorubicin-related cardiotoxicity in humans;[30] however, its use has been limited to adults with metastatic breast cancer who would benefit from additional doxorubicin treatment but in whom the cumulative dose of doxorubicin is already >300 mg/m^2.

In children treated with anthracyclines, ascertaining the long-term impact of dexrazoxane on clinical outcomes such as heart failure is difficult, given the limited length of follow-up and the progressive nature of anthracycline-related cardiac dysfunction. Nevertheless, sub-clinical cardiac outcomes such as changes in left ventricular structure and function and serum biomarker concentrations – for example, cardiac troponin T [cTnT] and NT-proBNP levels – were better in children treated with anthracyclines plus dexrazoxane than in those treated without dexrazoxane.[31,32]

Several large studies involving children with different tumour types treated with dexrazoxane have found similar results (Table 2). In particular, one study by the Dana–Farber Cancer Institute Acute Lymphoblastic Leukemia Consortium examined the cardioprotective effects of dexrazoxane in 206 children with high-risk acute lymphoblastic leukaemia. By the end of the doxorubicin therapy, concentrations of cTnT were elevated in 50% of the children treated with doxorubicin alone, but in only 21% of those treated with doxorubicin and dexrazoxane;[31] 5 years after the completion of the doxorubicin therapy, the cardioprotective benefits of dexrazoxane were predominant in girls, particularly with respect to changes in the left ventricular end-diastolic thickness-to-dimension ratio – a marker of pathologic left ventricular re-modelling – and left ventricular fractional shortening (Fig 4).

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Table 2. Summary of studies investigating the cardioprotective effects of dexrazoxane in children and adolescents with haematological or solid tumours receiving a chemotherapeutic regimen containing doxorubicin.

Reference	Patients	DOX and DRZ dosage	Results and comments
Wexler et al[48]	Sarcoma (⩽25 years)	DOX 50–70 mg/m^2 with (n = 18) or without (n = 15) DRZ (20:1 dose ratio)	Patients who received DRZ were less likely to experience sub-clinical cardiotoxicity (22 versus 67%; p < 0.01), had a smaller reduction in LVEF/100 mg/m^2 DOX (1.0 versus 2.7 percentages points; p = 0.02), and received a higher median dose of DOX
Lipshultz et al[31,]*	ALL (<18 years)	DOX 30 mg/m^2 with (n = 105) or without (n = 101) DRZ 300 mg/m^2	Elevated cTnT in 55 of 158 percentage points. Points on DOX alone were more likely to have elevated cTnT levels (50 versus 21%; p < 0.001) and extremely elevated cTnT levels (32 versus 10%; p < 0.001). Median follow-up was 2.7 years and event-free survival was 83% in both groups
Paiva et al[49]	Osteosarcoma (<28 years)	Untreated control group (n = 21) and DOX alone (mean dose 348 mg/m^2; n = 19) or DOX (mean dose 397 mg/m^2; n = 18) + DRZ (10:1 dose ratio)	Myocardial responses during low-dose dobutamine stress echocardiography in patients treated with DOX + DRZ were similar to those of patients not on chemotherapy and better than those treated with DOX alone. Both LVEF (8.3%) and LVFS (7.0%) were significantly (P ⩽ 0.02) lower in the DOX-only group versus the control group (13 and 11%) and DOX + DRZ group (13.2 and 11%). Patients treated with DRZ had better systolic performance than those on DOX alone, suggesting a cardioprotective effect
de Matos Neto et al[50]	Osteosarcoma (<21 years)	DOX 60–70 mg/m^2 with (n = 18) or without (n = 37) DRZ (20:1 dose ratio)	The cumulative dose of DOX was ~15% higher in the DRZ group versus the non-DRZ group. Systolic dysfunction was similar in the two groups, but the DRZ group had significantly (p = 0.03) better LV performance as assessed by the mean fractional shortening % at three follow-up visits [37.2 versus 35.7%; 38.5 versus 35.0%; and 38.2 versus 35.3%, respectively].
Lipshultz et al[32,]*	ALL (<18 years)	DOX 30 mg/m^2 with (n = 68) or without (n = 66) DRZ 300 mg/m^2	After 5 years, mean LVFS and LVESD Z scores were significantly worse than normal in the DOX group [−0.82 and 0.57, respectively], but not in the DOX + DRZ group [−0.41 and 0.15]
Choi et al[51]	Solid tumours (⩽14 years)	DOX 30 mg/m^2 with (n = 47) or without (n = 42) DRZ (10:1 dose ratio)	There were significantly fewer cardiac events with DOX + DRZ than with DOX (27.7 versus 52.4%; p = 0.02 at mean follow-up of 54 and 86 months, respectively). DOX + DRZ was also associated with less severe CHF (6.4 versus 14.3%; p = 0.049). 5-year cardiac event-free survival was 69.2% for DOX + DRZ and 45.8% for DOX (p = 0.04). DRZ reduced the incidence and severity of early and late anthracycline toxicity
Lipshultz et al[44,]*	ALL (high risk) (<18 years)	DOX 30 mg/m^2 with (n = 105) or without (n = 100) DRZ 300 mg/m^2	CT levels were increased 47 and 13% (p = 0.05) and NT-proBNP by 48 and 20% (p = 0.07) in the DOX-only and DOX + DRZ groups, respectively. The increases in CT were associated with abnormally reduced LV mass and end-diastolic posterior wall thickness-to-dimension ratio after 4 years (p < 0.01). Increases in BNP were related to abnormal LV thickness-to-dimension ratio, suggesting LV re-modelling after 4 years (p = 0.01). CT and BNP hold promise as biomarkers for anthracycline-induced cardiotoxicity
Kang et al[52]	Children with cancer (<18 years)	Anthracycline alone (n = 123) or combined with DRZ [low-dose, <100 mg/m^2, n = 85; high-dose, >100 mg/m^2, n = 50]	During chemotherapy, dose-limiting cardiotoxicity was significantly higher (p = 0.006) in the DOX-only group (7.3%) versus the high- (2.0%) and low-dose (0%) anthracycline groups treated with DRZ. In addition, LVEF and shortening fractions were greater in the low-dose anthracycline + DRZ group versus the anthracycline only group. Early use of DRZ protects against the development of cardiotoxicity during anthracycline therapy in children with cancer
Asselin et al[53,]**	ALL (T-cell) (⩽21 years)	DOX 30 mg/m^2 with (n = 273) or without (n = 264) DRZ 300 mg/m^2	After 3 years, Z-scores for LVFS (−0.05 versus −0.77), LV wall thickness (−0.13 versus −0.69) an LV thickness-to-dimension ratio (−0.09 versus −0.75) were better for the DRZ group versus the DOX control group. LVFS remained significantly improved in the DRZ group in a small number of patients after 4–6 years follow-up
Kopp et al[54,]***	Localised or metastatic osteosarcoma in children and adolescents	In patients with metastatic disease, DOX 375 mg/m^2; in patients with localised disease, DOX 450–600 mg/m^2. DRZ (10:1 dose ratio) was given for cardioprotection	None of the 47 patients with metastatic disease evaluated for cardiac effects showed clinical evidence of cardiotoxicity. In 242 patients with localised disease, one had a measurable serum cTnT level and one had clinical evidence of cardiotoxicity (grade 3). In this large group of patients with osteosarcoma, DRZ was an effective cardioprotectant
Shaikh et al[55]	Children treated for cancer and with DRZ as a cardiac protectant	Anthracycline alone or combined with DRZ. Systematic review limited information	In two of the five RCTs, DRZ was associated with improved shortening fraction Z-score (mean difference 0.61, p = 0.002) and thickness dimension Z-score (mean difference 0.66, p < 0.001). DRZ was associated with a reduction in clinical cardiotoxicity (relative risk 0.29, p = 0.001) and sub-clinical cardiotoxicity (relative risk 0.43, p < 0.001)

ALL = acute lymphoblastic leukaemia; BNP = brain natriuretic peptide; CHF = congestive heart failure; CT = cardiac troponin; cTnT = cardiac troponin T; DOX = doxorubicin; DRZ = dexrazoxane; ESD = end systolic dimension; LV = left ventricular; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVFS = left ventricular fractional shortening; NT-proBNP = N-terminal pro-brain natriuretic peptide; RCT = randomised clinical trial.

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*Protocol Dana-Farber 95-01

**Protocol POG 9404

***Protocol AOST0121 and POG9754

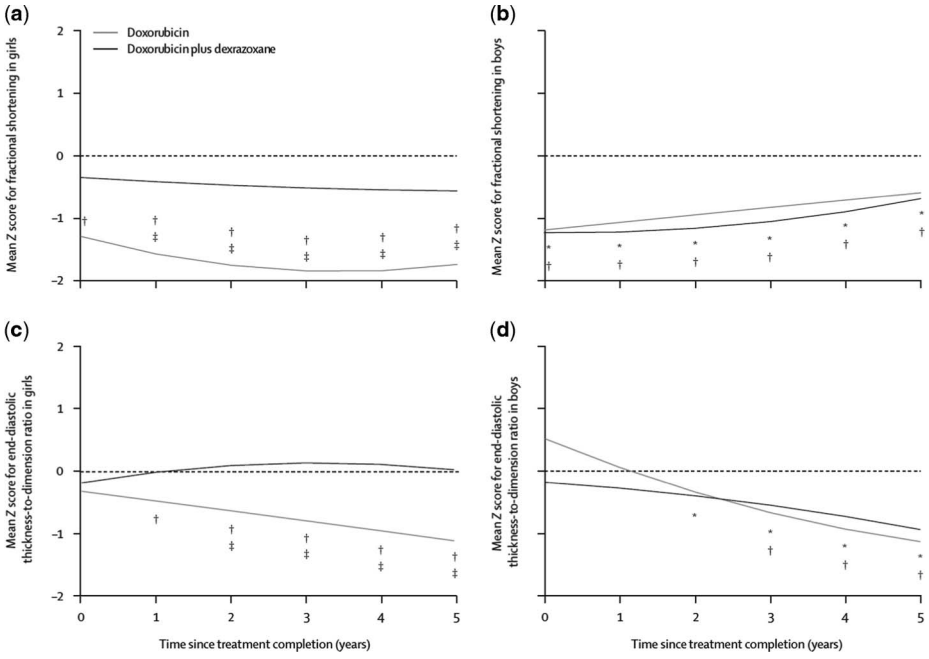

Figure 4.
*Mean left ventricular echocardiographic Z scores in boys and girls (n = 134). Plots are adjusted for age. *$p \leqslant 0.05$ for comparison of the mean Z score of the doxorubicin plus dexrazoxane group with zero; †$p \leqslant 0.05$ for comparison of the mean Z score for the doxorubicin group with zero and ‡$p \leqslant 0.05$ for comparisons of mean Z scores between the doxorubicin and doxorubicin plus dexrazoxane groups (Reprinted with permission from Elsevier[32]).*

This protective effect of dexrazoxane was once feared to extend to malignant cells, potentially leading to secondary malignancies,[33] but several other studies have found no such increase (Table 3).[34]

Enalapril has been tested as a cardioprotective agent in survivors who have received anthracycline therapy. One study found that treatment with enalapril resulted in an early decrease in left ventricular end systolic wall stress;[35] however, Lipshultz et al. found that these beneficial effects of enalapril on cardiac function were transient and were largely related to how changes in blood pressure reduced left ventricular wall stress.[36] Thus, the long-term effects of enalapril as a cardioprotectant are yet to be determined.

Based on studies that have found higher dose rates of doxorubicin to be associated with cardiotoxicity in children, continuous doxorubicin infusion was hypothesised to provide some cardioprotection by lowering peak serum concentrations of the drug.[37] In addition, continuous infusion of doxorubicin does reduce the risk of cardiotoxicity in adults.[38] As a result, paediatric protocols began to incorporate continuous infusion, despite the lack of evidence for long-term cardioprotection. In a multi-centre, randomised trial of children with high-risk acute lymphoblastic leukaemia, 8 years after diagnosis, neither cardioprotection nor event-free survival was better in children who received doxorubicin as a continuous infusion compared with a bolus infusion.[39] Both groups had similar values of abnormal left ventricular function and structure. In addition, 10-year event-free survival was not significantly different – 83 and 78% for continuous and bolus doxorubicin infusions, respectively – suggesting no effect on efficacy.[39] In another study of anthracycline-treated childhood cancer survivors, a mean of 7 years after treatment, 20% of the bolus group and 11% of the continuous infusion group had reduced cardiac function, but the difference was not statistically significant.[40] Despite the lack of definitive evidence of cardioprotection and the higher hospital length of stay, costs, and the risks of thromboembolic events and mucositis, continuous infusion is still incorporated into paediatric treatment protocols for cardioprotection.[41]

Surveillance of cardiotoxicity

Conventional methods for monitoring heart function, such as echocardiography, radionuclide ventriculography, and cardiac MRI, detect changes only after a certain degree of damage has already occurred. Thus, detecting cardiotoxicity before irreversible damage has occurred is challenging. Newer imaging modalities such as myocardial strain and strain rate have

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Table 3. Summary of studies investigating the development of second malignant neoplasms in children and adolescents with haematological or solid tumours treated with a chemotherapy regimen containing doxorubicin, with or without dexrazoxane.

Reference	Patients	DOX and DRZ dosage	Results and comments
Tebbi et al[33,******]	HD (⩽25 years)	DOX 25–30 mg/m^2 (ABVE) alone (n = 239) or with DRZ 300 mg/m^2 (n = 239)	Median follow-up 58 months, 4-year CIRs: all SMNs [DOX 0.85 ± 0.6% DOX + DRZ 3.43 ± 1.2% (p = 0.06)]; AML/MDS [DOX 0.85 ± 0.6% DOX + DRZ 2.55 ± 1.0% (p = 0.16). Adding DRZ to DOX to chemotherapy may increase risk for SMNs
Barry et al[56,*]	ALL (high-risk) (<18 years)	DOX chemotherapy 30 mg/m^2 with (n = 105) or without (n = 100) DRZ	Median follow-up 6.2 years, the 5-year CIR for SMNs was zero for the DOX + DRZ group with no significant difference between the two groups. DRZ was not associated with an increased risk for SMNs
Schwartz et al[57,***]	Intermediate- and high-risk HD (<22 years)	DOX 30 mg/m^2 with (n = 107) or without (n = 109) DRZ 300 mg/m^2	SMNs occurred in 3/107 patients in the DRZ group and 1/109 patients in the DOX control group
Salzer et al[58,**]	ALL (T-cell) (<22 years)	DOX with (173) or without (159) DRZ	The CIR for SMNs after 5 and 10 years, respectively, was 1.3 and 1.3%, in the DOX control group and 2.3 and 4.2% in the DRZ group (p = 0.15)
Vrooman et al[59,*******]	ALL (high or very-high risk <18 years). Pooled analysis (three studies including Barry et al[56])	DOX 30 mg/m^2 with DRZ 300 mg/m^2 (n = 553)	After 3.8 years median follow up (with a range from 0.2 to 13.6 years) mean (SD) overall estimated cumulative incidence of SMNs was 0.24% [0.24%] (95% CI 0.02–1.29%). Thus, in a large population of children with high-risk ALL who received DRZ as a cardioprotectant, the occurrence of SMNs was rare
Tebbi et al[60,****]	HD (low-risk) (⩽21 years)	DOX 25 mg/m^2 with (n = 127) or without (n = 128) DRZ 250 mg/m^2	There were five primary SMNs and three occurred after relapse. Of the five primary SMNs, four occurred in the DRZ group and one in the DOX control group. The authors attributed the difference to the concomitant use of three topoisomerase II inhibitors (including etoposide) rather than to one specific agent
Seif et al[61]	Children with newly diagnosed cancer other than AML in the PHIS database	All children receiving anthracyclines were followed and exposure to DRZ and secondary AML monitored	Of 15,532 children in the cohort exposed to anthracyclines, 1406 received DRZ. The rate for secondary AML was 0.21% in the DRZ group and 0.55% in the group not receiving DRZ. DRZ was not associated with an increased risk of secondary AML
Chow et al[62,*****]	ALL (n = 537), advanced HD (n = 216), low or intermediate HD (n = 255). Pooled analysis (Tebbi et al[60],[33]; Salzer et al[58])	DOX 100–360 mg/m^2 with (n = 507) or without DRZ (10:1 dose ratio; n = 501)	With a median follow-up of about 8 years, DRZ + DOX was not associated with an increased risk of second cancers versus DOX alone (10 versus 9; hazard ratio, 1.08; 95% CI 0.44–2.67)
Asselin et al[53,**]	ALL (T-cell) (⩽21 years)	DOX 30 mg/m^2 with (n = 273) or without (n = 264) DRZ 300 mg/m^2	11 SMNs were recorded; eight in the DRZ group and three in the DOX control group (p = 0.17). At 5 years the mean cumulative incidences were 0.7 ± 0.5 versus 0.8 ± 0.5% and at 10 years 1.8 ± 0.9 versus 1.2 ± 0.7%, respectively. DRZ was not associated with an increased risk of SMNs
Kopp et al[54,********]	Localised or metastatic osteosarcoma in children and adolescents	In patients with metastatic disease, DOX 375 mg/m^2, and in those with localised disease, DOX 450–600 mg/m^2. DRZ (10:1 dose ratio) was given for cardioprotection	SMNs occurred in 3 of 96 patients with metastatic disease and 2 of 272 patients with localised disease. In all, 5/398 patients (1.4%) had SMNs, which compares favourably with the historical rate of 1–2% in the centres involved in the study
Shaikh et al[55]	Children with cancer treated with DRZ	Anthracycline alone or combined with DRZ. Systematic review with limited information	In five RCTs there were 16/625 (2.5%) SMNs with DRZ versus 6/619 (1.0%) SMNs without DRZ (p = 0.06). In NRSs, there were 6/860 (0.7%) with DRZ versus 18/1,825 (1.0%) SMNs without DRZ (p = 0.06).

ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia; CI = confidence interval; CIR = cumulative incidence rate; DOX = doxorubicin; DRZ = dexrazoxane; HD = heart disease; MDS = myelodysplastic syndrome; NRSs = non-randomised studies; RCTs = randomised clinical trials; SMN = second malignant neoplasm

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*Protocol Dana–Farber 95-01

**Protocol POG 9404

***Protocol POG 9425

****Protocol POG 9426

*****Protocols POG 9404, POG9425, and 9429

******Protocol POG 9425 and 9426

*******Protocols 95-01, 00-01, and 05-01

********Protocols POG9754 and AOST 0121

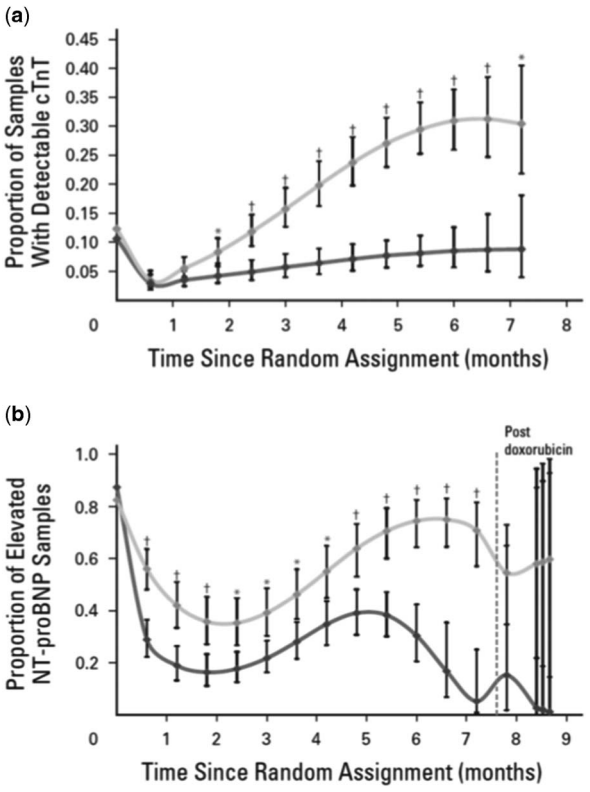

Figure 5.
*Model-based estimated probability of having (**a**) an increased cTnT level and (**b**) an increased NT-proBNP at each depicted time point in patients treated with doxorubicin, with or without dexrazoxane. Increased cTnT is defined as a value >0.01 ng/ml. Increased NT-proBNP is defined as a value ⩾150 pg/ml for children younger than 1 year and a value ⩾100 pg/ml for children aged 1 year or older. The doxorubicin–dexrazoxane group is indicated by the blue line and the doxorubicin group by the gold line. Vertical bars show 95% CIs. *p value versus dexrazoxane group ⩽0.05 and †p value versus dexrazoxane group ⩽0.001. An overall test for dexrazoxane effect of cTnT during treatment was significant ($p < 0.001$). An overall test for dexrazoxane effect of NT-proBNP during treatment was significant ($p < 0.001$) and after treatment was not significant ($p = 0.24$) (Reprinted with permission from the American Society of Clinical Oncology[44]). CI = confidence interval; cTnT = cardiac troponin T; NT-proBNP = N-terminal pro-brain natriuretic peptide.*

limited specificity to detect myocardial injury.[42] Strain and strain rate depend on loading conditions, which are often disturbed in cancer patients. Thus, more studies are needed to determine the clinical utility of these modalities for detecting clinically important cardiotoxicity in childhood cancer survivors.

In addition to the imaging modalities mentioned above, serum cardiac biomarker concentrations that have been validated as surrogates for late cardiac status in this population might also prove to be useful.[43] Elevated serum concentrations of cTnT, an indicator of myocardial damage, and N-terminal pro-brain natriuretic peptide (NT-proBNP), produced in response to pressure overload and stretching, have been studied extensively in childhood cancer survivors.[31,43,44] In a study of children with high-risk acute lymphoblastic leukaemia, elevated concentrations of serum cTnT during the first 90 days of anthracycline therapy were associated with reduced left ventricular mass and left ventricular end-diastolic posterior wall thickness and increased left ventricular pathologic re-modelling 5 years later (Fig 5a).[44] In that same study, elevated serum concentrations of NT-proBNP in the first 90 days of therapy were also associated with an abnormal left ventricular thickness-to-dimension ratio, suggesting left ventricular pathologic re-modelling 4 years later (Fig 5b);[44] however, before, during, and after treatment, the percentage of patients with elevated serum NT-proBNP concentrations was higher than the percentage with elevated cTnT concentrations, indicating that NT-proBNP may detect cardiac stress before irreversible myocardial damage has occurred.[44] This relationship, if validated, may have implications for identifying early cardiac damage in at-risk children, when prevention or cardiac treatment may be most successful.

Despite receiving the same cumulative doses, or even having similar risk factors, cardiotoxicity does not affect patients equally. Some might never experience any kind of cardiac dysfunction, whereas others might experience heart failure. Owing to this variation, there is a growing interest in the potential of genetic markers to identify high-risk patients. Preliminary studies have found that patients exposed to low-to-moderate doses of anthracyclines who express the G allele of the *CBR3* gene, which encodes carbonyl reductase 3, have an increased risk for cardiomyopathy.[45] Another study explored the genetic pre-disposition for iron overload, hereditary haemochromatosis, in survivors treated with doxorubicin. On the premise that doxorubicin–iron complexes generate doxorubicin semiquinone free radicals, which then lead to lipid peroxidation and DNA damage, investigators screened 184 survivors of high-risk acute lymphoblastic leukaemia for the frequency of hereditary haemochromatosis gene mutations – C282Y and H63D.[46] In the 10% of children carrying a mutation in the hereditary haemochromatosis C282Y allele, the risk for doxorubicin-related myocardial injury was nine times as high as that of non-carriers.[46] Although validation studies are required, screening for these genetic mutations may prove useful for guiding treatment and in post-chemotherapy monitoring.

With more childhood cancer survivors now reaching adulthood, it is vital to understand the adverse effects of cancer treatment on the cardiovascular system and their long-term consequences to

https://doi.org/10.1017/S1047951115000906 Published online by Cambridge University Press

identify and establish optimal prevention and management strategies that balance oncologic efficacy with long-term safety.[47]

Acknowledgement

None.

Financial Support

Dr Steven Lipshultz was also supported in part by grants from the National Institutes of Health (HL072705, HL078522, HL053392, CA127642, CA068484, HD052104, AI50274, HD052102, HL087708, HL079233, HL004537, HL087000, HL007188, HL094100, HL095127, and HD80002), the Children's Cardiomyopathy Foundation, the Women's Cancer Association of the University of Miami, the Lance Armstrong Foundation, the STOP Children's Cancer Foundation, the Scott Howard Fund, and the Michael Garil Fund. Vivian Franco was supported by the Michael Garil Fund.

Conflicts of Interest

Steven Lipshultz was a paid consultant to The Clinigen Group to help organise the expert panel on cardio-oncology in Newark, NJ, in July, 2014. There are no other relevant conflicts of interest to disclose.

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