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Cranial Irradiation as an Additional Risk Factor for Anthracycline Cardiotoxicity in Childhood Cancer Survivors: An Analysis from the Cardiac Risk Factors in Childhood Cancer Survivors Study

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Abstract

Background—Anthracycline-treated childhood cancer survivors suffer cardiac damage that results in decreased left ventricular (LV) mass, leading to increased LV wall stress, which underlies their greater risk of cardiomyopathy. Many of these survivors are also at risk of growth hormone (GH) abnormalities from cranial irradiation exposure though it is unknown if such exposure is associated with cardiotoxicity.

Methods—Echocardiograms and insulin-like growth factor-1 (IGF-1), a marker of GH, were measured in 130 anthracycline-treated childhood cancer survivors, 59 of whom had been exposed to cranial irradiation, a mean 10 years from cancer diagnosis. Echocardiographic parameters and IGF-1 were standardized relative to age or body-surface area using data from sibling controls and expressed as the percent difference from normal.

Results—After adjusting for other risk factors, survivors exposed to cranial irradiation had an additional 12% decrease in LV mass compared to unexposed survivors ($P<.01$), and an additional 3.6% decrease in LV dimension ($P=.03$). Survivors exposed to cranial irradiation also had a 30.8% decrease in IGF-1 relative to normal, which was greater than the 10.5% decrease in unexposed survivors ($P<.01$).

Conclusions—In anthracycline-treated childhood cancer survivors, a mean 10 years from diagnosis, those with cranial irradiation exposure had significantly greater decreases in LV mass and dimension. Because cranial irradiation was also associated with decreased IGF-1, it is possible that GH deficiencies mediated this effect suggesting that GH replacement therapy may help prevent the development of cardiotoxicity.

Keywords

Cardiomyopathy; Anthracyclines; Cranial Irradiation; Cancer; Survivors

Every year, more than 12,000 children in the United States are diagnosed with cancer and as many as 80% of these children attain a 5-year oncologic event-free survival [1, 2]. It is hoped that these survivors will go on to lead normal, healthy lives, though by thirty years after their original cancer diagnosis, over 70% will have developed a chronic health condition caused by complications of cancer therapies, such as radiation and chemotherapy [3–6]. Chief among major complications is cardiac disease, which is the leading cause of serious, non-cancer related morbidity and mortality in survivors [7, 8].

Anthracyclines, used to treat more than half of childhood cancer patients, are currently indispensable, given their oncologic efficacy [9]. However, anthracycline cardiotoxicity is a serious complication that can result in heart failure, heart transplantation, and cardiac death [10]. Chronic cardiotoxicity, defined as a presentation at least 1 year after cancer treatment, is common and can occur even after treatment with a low anthracycline cumulative dose [11–16]. Within 10 years after cancer diagnosis, more than half of survivors treated with anthracyclines have echocardiographic evidence of abnormal cardiac structure and function [13, 14].

Anthracycline cardiotoxicity characteristically results from myocardial cell death that leads to decreased left ventricular (LV) mass and LV wall thickness [17, 18]. This reduced thickness can increase the stress on the remaining LV wall as it tries to generate sufficient cardiac output, and these changes can be progressive, even a decade after treatment. Over time, if compensation becomes inadequate, the stress can result in LV dysfunction. Risk factors for cardiotoxicity include younger age at diagnosis, longer time from diagnosis, anthracycline dose rate and cumulative dose, concomitant cardiac irradiation, and female sex [10, 19]. There are currently no long-term effective treatments although identifying additional risk factors may lead to new treatment strategies and assist in risk prediction.

Cranial irradiation, used to treat childhood leukemia and brain cancers and to prevent brain metastases, is another common treatment for childhood cancers. Cranial radiation exposure damages the hypothalamic-pituitary axis [20]. One of the first complications of such damage is growth hormone (GH) deficiency, which can occur after relatively low radiation exposures [21, 22]. Children with GH deficiency from other causes have decreased LV mass that improves with GH replacement therapy [23–25]. GH has marked cardiac effects and has even been tested as a cardiac treatment in children and adults without GH deficiency [26–28].

The cardiac effects of cranial irradiation-induced GH deficiency in patients treated with anthracyclines are not well understood. Prior studies have often lacked a control group of anthracycline-treated survivors who were not exposed to cranial irradiation [29–32]. It is possible that GH deficiency exacerbates LV dysfunction in anthracycline-treated survivors. The potential for a continued effect of cranial irradiation on cardiotoxicity through GH deficiency is consistent with the progressive nature of the cardiac damage from anthracyclines and further supports examining this relationship.

We sought to determine whether cranial irradiation was associated with anthracycline cardiotoxicity by examining anthracycline-treated childhood cancer survivors from the National Cancer Institute-funded Cardiac Risk Factors in Pediatric Cancer Survivors Study (CRG) [33]. We hypothesized that anthracycline-treated survivors exposed to cranial irradiation would show greater cardiotoxicity than unexposed survivors and that insulin-like growth factor-1 (IGF-1), a marker of GH functioning, would be more strongly associated with cardiac abnormalities in exposed than in unexposed survivors.

METHODS

The CRG included survivors recruited from the Pediatric Long-Term Survivor Clinic at the University of Rochester between 1998 and 2003. The clinic provides care for survivors in a catchment area consisting of the Finger Lakes region of New York State and northern Pennsylvania. To capture survivors not receiving care in this clinic, hospital records were reviewed for patients treated for childhood cancer at the University of Rochester. Eligible survivors had received a cancer diagnosis 3 or more years earlier, were no longer receiving chemotherapy or radiation, and were without active cancer. This study, which uses data from the CRG, included only those survivors from the CRG study who had been treated with anthracyclines. These survivors were grouped by their exposure to cranial irradiation. Two survivors, both in the cranial irradiation exposure group, who had received GH replacement therapy, were excluded.

In brief, the CRG collected information on cancer diagnosis and treatment from the medical records. All other information, including echocardiograms, phlebotomy, anthropomorphic measurements, and demographics, was collected during a single, daylong study visit. A cardiologist and sonographer blinded to subject characteristics read 2-dimensional and Doppler echocardiograms and measured LV parameters. IGF-1 was measured from fasting serum samples. For survivors younger or older than 20 years, BMI was classified using CDC growth charts or standard definitions, respectively, as underweight ($<5\%$ or $<18.5 \text{ kg/m}^2$), normal (5 to 85% or 18.5 to 24.9 kg/m^2), overweight (85 to 95% or 25 to 29.9 kg/m^2), or obese ($>95\%$ or $>30 \text{ kg/m}^2$) using CDC growth charts for survivors younger than 20 years.

Demographic characteristics were compared using Fisher's exact test for categorically measured variables and the Wilcoxon rank-sum test for continuously measured variables.

Because normal values for LV parameters vary with aging and somatic growth, echocardiographic data from a sibling control group ($n = 76$) was used to assess how the values of survivors differed from development-specific normal values (Appendix, Video 1). For each echocardiographic parameter, a series of power regression models were fit to the sibling control data with the adjusted R^2 statistic used to select the best fitting model, similar to the methodology used by Colan et al. to obtain equations to generate Z scores [34]. For models of structural parameters (LV mass, LV end-systolic wall thickness, and LV end-diastolic dimension), the dependent variables included sex and body-surface area. For models of the functional parameters (LV end-systolic wall stress and LV fractional shortening), the dependent variables included sex and age. Selected models were used to generate normal predicted echocardiographic parameter values for each survivor based on sex and either body-surface area or age. The actual echocardiographic parameter values of the survivors were compared to the normal predicted values and expressed as the percent difference from normal, and these values were used for subsequent analyses.

Because normal values for IGF-1 also vary during aging, IGF-1 values from the sibling control group were used to assess how the values of survivors differed from age-specific normal values (Appendix, Video 2). The IGF-1 values of the sibling control group were first graphed over age by sex. This relationship appeared to most closely resemble a quartic function with IGF-1 increasing in the age range associated with puberty and then decreasing, leveling off, and remaining somewhat constant throughout the age range of subjects in the CRG. This was supported empirically by the quartic regression having the largest adjusted R^2 statistic when compared with quadratic and cubic regression models. This model was then used to generate normal predicted IGF-1 values for each survivor based on sex and age. The actual IGF-1 values of the survivors were compared to the normal predicted values and

expressed as the percent difference from normal and these values were used for subsequent analyses. This same process was repeated to determine the percent difference in height from age- and sex-specific normal predicted values, based on the sibling control data and assuming a cubic relationship with age.

LV parameter values were compared between cranial irradiation exposure groups using the Wilcoxon rank-sum test. Because other factors are known to affect LV parameters, linear regression models were used to estimate the mean difference in LV parameters for anthracycline-treated survivors exposed and unexposed to cranial irradiation adjusted for gender, cardiac irradiation exposure, cumulative anthracycline dose, age at diagnosis, and time from diagnosis. Unadjusted models with cranial irradiation exposure as the only independent variables were also used. Because the distribution of BMI classifications differed between exposure groups, additional analyses adjusting for BMI were conducted to assess its impact on the results above and were consistent with other analyses.

IGF-1 and height were compared between groups using the Wilcoxon rank-sum test. The association between LV parameters and IGF-1 in anthracycline-treated survivors exposed to cranial irradiation was assessed using Spearman's Rho.

Finally, all analyses involving LV parameters were repeated with the LV parameter values expressed as age- or body surface area-adjusted Z scores, calculated relative to a standard population [34, 35]. The Z scores were calculated by dividing the difference between a survivor's observed value and the normal predicted value, based on the standard population, by the standard deviation of the normal predicted values. The standard population consisted of 285 subjects from Children's Hospital Boston whose ages were similar to those of the survivors included in the present study. These results were consistent with those resulting from analyses in which LV parameters were expressed as the percent difference from normal, relative to the sibling controls (Appendix).

Data were analyzed using Stata 11.2 (StataCorp LP; College Station, TX). When necessary, transformations were made to meet normality assumptions, and estimates back-transformed for reporting. Alpha was set at .05, all P values are two-sided and no adjustments were made for multiple hypothesis testing. This study had appropriate institutional review-board approvals and written informed consent.

RESULTS

The CRG cohort consisted of 201 childhood cancer survivors, 130 of whom were treated with anthracyclines and had not received GH replacement therapy. Of these 130 survivors, 59 had received exposure to cranial irradiation and 71 were unexposed (Table I). Cranial irradiation exposure ranged from 6 Gy to 100 Gy with the median exposure being 18 Gy, and only 3 survivors receiving more than 30 Gy. In total, 5 of these included survivors reported having received a heart failure diagnosis at some point (2 in the exposed group and 3 in the unexposed group).

Exposed and unexposed survivors had similar mean ages at cancer diagnosis (7.0 vs. 7.6 years, $P=NS$) and similar mean times since diagnosis (10.3 vs. 10.5 years, $P=.95$). The exposed group contained a lower proportion of females (42% vs. 62%, $P=.03$) and a lower proportion of survivors receiving cardiac irradiation exposure (22% vs. 32%, $P=NS$) but had received a higher mean cumulative dose of anthracyclines (296 vs. 244 mg/m^2 , $P<.01$). The exposed group also contained a higher proportion of survivors diagnosed with leukemia (80% vs. 20%, $P<.01$).

Compared to unexposed survivors, exposed survivors had significantly decreased LV mass and LV end-diastolic dimension and non-statistically significantly decreased LV end-systolic wall thickness and increased LV wall stress (Figure 1). Both cranial irradiation exposure groups had similar LV fractional shortening.

After adjusting the difference in LV parameters for age at diagnosis, length of time since diagnosis, sex, cardiac irradiation exposure, and cumulative anthracycline dose, LV mass was still decreased by an additional 12% relative to normal and LV dimension by 3.6% relative to normal in the cranial irradiation-exposed survivors compared to the unexposed survivors (Table II). Cranial irradiation-exposed survivors also had additional decreases relative to normal in LV wall thickness of 2.5% and increases in LV afterload of 1.8% compared to the unexposed survivors, but these differences were not statistically significant.

Compared to survivors unexposed to cranial irradiation, those exposed to cranial irradiation also had a statistically significantly decreased IGF-1 relative to normal (median, -30.8% vs. -10.5% ng/mL, $P<.001$) and also had statistically-significantly decreased height relative to normal (median, -5.0% vs. -1.3%, $P<.001$) (Figure 2).

In survivors exposed to cranial irradiation, IGF-1 was weakly associated or not associated with LV parameters (Figure 3).

DISCUSSION

In anthracycline-treated childhood cancer survivors from the CRG, cranial irradiation exposure was significantly associated with decreased LV mass and LV end-diastolic dimension and a non-statistically significantly decreased LV end-systolic wall thickness and increased LV end-systolic wall stress. These same cranial irradiation-exposed survivors had decreased IGF-1, a marker of GH deficiency.

Cranial irradiation was associated with an additional decrease in LV mass relative to normal of 12% in anthracycline-treated survivors. This decreased LV mass appears to be the result of GH abnormalities which is consistent with the decrease in LV mass seen in patients with GH deficiency not related to cranial irradiation [23, 24]. Further, the weak association between IGF-1 and LV mass may be consistent with the increases in LV wall thickness and mass reported in studies of anthracycline-treated survivors given GH replacement therapy [30, 31].

Cranial irradiation was also associated with an additional decrease relative to normal of roughly 3% in LV wall thickness and 4% in LV dimension, which underlie the relationship with decreased LV mass. LV wall thickness was moderately associated with IGF-1, which may be reflected in the additional increase relative to normal of 2% in LV afterload. This provides some evidence that the structural abnormalities associated with cranial irradiation may have functional consequences consistent with the anthracycline cardiotoxicity pathway [16,18]. While decreased LV dimension is not usually viewed as problematic, this may not be true for patients with the restrictive-like pattern of anthracycline cardiotoxicity [17, 18]. For these patients, in which the LV may have difficulty relaxing during diastole, a smaller chamber size may serve as an additional limitation to LV filling and further impair cardiac output. This association is also consistent with other studies that have found GH deficient children have decreased LV dimension and volume relative to controls [24, 44] and that LV dimension increases with GH replacement [23, 45].

Cranial irradiation exposure was not associated with LV fractional shortening, and there was no association between IGF-1 and LV fractional shortening among those exposed to cranial irradiation. This finding may reflect that the changes in LV structure associated with cranial

irradiation exposure are not related to cardiac functioning. Two prior studies examining the impact of GH replacement therapy in anthracycline-treated survivors found no effect on LV fractional shortening, though therapy was initiated several years after cranial irradiation exposure in both studies [30, 31]. The lack of an association in this study could also be due to limited follow-up and the chronic nature of anthracycline cardiotoxicity. At less than 10 years from treatment, the heart may still be capable of compensating for structural abnormalities. This possibility is consistent with reports that LV fractional shortening begins to decline markedly after 10 years, the same time at which the incidence of heart failure continues to increase [7, 13].

The strength of the association between IGF-1 and LV parameters in the anthracycline-treated survivors exposed to cranial irradiation was only weak to moderate. However, this is expected given that other factors such as anthracycline dose, age at diagnosis, cardiac irradiation, and sex explain substantial portions of the variation in anthracycline cardiotoxicity [10, 19]. It is important to note that even after adjusting for these other factors, survivors with cranial irradiation exposure still had statistically significant worse abnormalities in LV structure. Having a more complete understanding of the risk factors underlying anthracycline damage might help produce clinically useful risk prediction models [36].

Although LV parameters and IGF-1 were standardized relative to a sibling control group to adjust for the effects of aging and growth on the normal values of these variables, measurements of abnormalities may still contain some error. For LV parameters, analyses were repeated with abnormalities determined relative to a standard population and yielded consistent results (Appendix) [34]. In addition to helping confirm the relationship between cranial irradiation and LV structure, the similarity of these results also helps validate the use of this standard population to measure development-specific abnormalities, which is needed when a control group is unavailable. Because these measures were created to describe the LV parameters of both survivors exposed and unexposed to cranial irradiation, measurement error is less likely to have introduced bias.

Error in measuring abnormalities in IGF-1 may have reduced the ability to determine if variation in hypothalamic-pituitary axis damage is associated with cardiac abnormalities in anthracycline-treated survivors. It is possible that the reported associations are actually underestimates of the true association between IGF-1 and LV structure and function in this population. Also relevant to interpreting these results are the limited sample size and low power to detect statistically significant relationships. Given the relative rarity of childhood cancer, identifying large numbers of anthracycline-treated survivors both exposed and unexposed to cranial irradiation and obtaining detailed clinical measurements, such as echocardiograms, is often not feasible. Finally, variation in the cancer diagnoses of exposed and unexposed survivor groups was present but has not been previously found to have an independent association with cardiotoxicity and was not a focus of this study looking at the effect of a particular cancer therapy. Additionally, the two groups were not perfectly balanced with respect other exposures including cumulative anthracycline dose which is a known predictor of anthracycline cardiotoxicity. Differences between the groups persisted even after statistical adjustment for these potential confounders. However, the potential for residual confounding or confounding by unmeasured variables cannot be excluded given the exposure of interest was not randomly assigned.

Although not examined in this study, cranial irradiation is associated with having traditional risk factors for cardiovascular disease, such as obesity and dyslipidemia, and may be one mechanism by which survivors are at increased risk of cardiovascular disease [8, 37–40]. Taken together, it is possible that GH replacement therapy could reduce the burden of

cardiovascular disease in survivors by improving both cardiac structure and cardiometabolic health. Although concerns over cancer recurrence and second malignancies have limited the use of GH replacement therapy, recent evidence indicates that this risk is low or possibly non-existent [41–43]. And while prior studies have not shown sustained improvements in cardiac function with GH replacement therapy, these studies started therapy years after cranial irradiation exposure and after irreversible GH-related cardiac damage may have already occurred. Additionally, these studies have shown temporary improvements in LV wall thickness, mass, and systolic blood pressure [30].

In conclusion, anthracycline-treated childhood cancer survivors exposed to cranial irradiation have abnormal cardiac structure that may worsen over time. These abnormalities appear to be associated with decreased GH functioning and thus may be treatable using GH replacement therapy. Future studies should seek to determine whether the improvements in cardiac structure and cardiometabolic health expected to occur with GH replacement therapy outweigh any possible complications of this therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Box plots of the distribution of left ventricular (LV) parameters of 130 childhood cancer survivors treated with anthracyclines by exposure to cranial irradiation (CR). LV parameters included mass, end-systolic posterior wall thickness (wall thickness), end-diastolic dimension (dimension), end-systolic wall stress (afterload), and fractional shortening. All LV parameters are expressed as % change relative to normal. The Wilcoxon rank-sum test was used to compare the LV parameters across CR exposure groups with the resulting P values reported.

Figure 2.

Box plots of the distributions of IGF-1 and height of 130 childhood cancer survivors treated with anthracyclines by exposure to cranial irradiation (CR). IGF-1 and height expressed as the % change relative to normal. P values reported based on Wilcoxon rank-sum test.

Figure 3.

Scatter plots depicting the association between IGF-1 and left ventricular (LV) parameters in 59 childhood cancer survivors treated with anthracyclines and exposed to cranial irradiation. LV parameters included mass, end-systolic posterior wall thickness (wall thickness), end-diastolic dimension (dimension), end-systolic wall stress (afterload), and fractional shortening. All LV parameters and IGF-1 are expressed as % change relative to normal. Spearman's Rho was used to assess the association between LV parameters and IGF-1, with P values reported, and a linear trend line has been added.

Table I

Characteristics of 130 anthracycline-treated childhood cancer survivors and exposed or unexposed to cranial irradiation

Characteristic	Cranial irradiation		P
	Exposed (n = 59)	Unexposed (n = 71)	
	n (%)	n (%)	
Sex			
Male	34 (58)	27 (38)	.03
Female	25 (42)	44 (62)	
Age at time of study (years)			
6 to 12	15 (25)	19 (27)	NS
13 to 19	29 (49)	25 (36)	
20 to 37	15 (25)	26 (37)	
BMI classification at time of study (kg/m ²)			
Underweight	5 (8)	1 (1)	.08
Normal	32 (54)	42 (60)	
Overweight	9 (15)	18 (26)	
Obese	13 (22)	9 (13)	
Cancer type			
Leukemia	47 (80)	14 (20)	<.01
Lymphoma	7 (12)	22 (31)	
Sarcoma	1 (2)	12 (17)	
Brain	1 (2)	0 (0)	
Other	3 (5)	23 (32)	
Age at diagnosis (years)			
0 to 5	34 (58)	33 (46)	NS
6 to 12	17 (29)	20 (28)	
Older than 12	8 (14)	18 (25)	
Time from diagnosis (years)			
3 to 9	32 (54)	38 (54)	NS
10 to 16	20 (34)	26 (37)	
17 to 31	7 (12)	7 (10)	
Cumulative anthracycline dose (mg/m ²)			
45 to 240	18 (31)	35 (51)	<.01
241 to 360	13 (22)	24 (35)	
360	28 (47)	10 (14)	
Cardiac irradiation treatment			
Yes	13 (22)	23 (32)	NS
No	46 (78)	48 (68)	
Cranial irradiation dose (gy)			
0 to 18	39 (66)	--	
>18 to 30	9 (15)	--	

Characteristic	Cranial irradiation		P
	Exposed (n = 59)	Unexposed (n = 71)	
	n (%)	n (%)	
>30 to 59.9	2 (3)	--	
60	1 (2)	--	
Total body irradiation	8 (14)	--	--

Table II

Adjusted difference in left ventricular parameters of 130 anthracycline-treated childhood cancer survivors by exposure to cranial irradiation

LV parameter	Unadjusted difference*	P	Adjusted difference*	P
Mass	−12.0%	<.01	−12.0%	<.01
Wall thickness	−2.1%	NS	−2.5%	NS
Dimension	−3.0%	.06	−3.6%	.03
Afterload	+2.6%	NS	+1.8%	NS
Fractional shortening	−0.2%	NS	−0.7%	NS

* Differences in the LV parameters are measured as the percent change from normal between the cranial irradiation exposed and unexposed groups and calculated as the exposed group minus the unexposed group. Separate linear regression models were fit for each left ventricular (LV) parameter [mass, end-systolic posterior wall thickness (wall thickness), end-diastolic dimension (dimension), end-systolic wall stress (afterload), and fractional shortening], with the parameter as the dependent variable. The unadjusted model included only cranial irradiation as an independent variable while the adjusted model included the following independent variables: cranial irradiation, gender, cardiac irradiation exposure, cumulative anthracycline dose, age at diagnosis, and time from diagnosis.