

FEMALE SEX AND HIGHER DRUG DOSE AS RISK FACTORS FOR LATE CARDIOTOXIC EFFECTS OF DOXORUBICIN THERAPY FOR CHILDHOOD CANCER

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Abstract *Background.* Late cardiotoxic effects of doxorubicin are increasingly a problem for patients who survive childhood cancer. Cardiotoxicity is often progressive, and some patients have disabling symptoms. Our objective was to identify risk factors for late cardiotoxicity.

Methods. We examined echocardiograms from 120 children and adults who had received cumulative doses of 244 to 550 mg of doxorubicin per square meter of body-surface area for the treatment of acute lymphoblastic leukemia or osteogenic sarcoma in childhood, a mean of 8.1 years earlier. Measurements of blood pressure and left ventricular function, contractility (measured as the stress-velocity index), end-diastolic posterior-wall thickness, end-diastolic dimension, mass, and afterload (measured as end-systolic wall stress) were compared with sex-specific values from a cohort of 296 normal subjects.

Results. All echocardiographic measurements were abnormal at follow-up a minimum of two years after the end of therapy, with more frequent and severe abnormal-

ities in female patients. In a multivariate analysis, female sex and a higher cumulative dose of doxorubicin were associated with depressed contractility ($P \leq 0.001$), and there was an interaction between these two variables. Independent and significant associations were found between a higher rate of administration of doxorubicin and increased afterload ($P \leq 0.001$), left ventricular dilatation, and depressed left ventricular function; between a higher cumulative dose and depressed left ventricular function ($P \leq 0.001$); between a younger age at diagnosis and reduced left-ventricular-wall thickness and mass and increased afterload; and between a longer time since the completion of doxorubicin therapy and reduced left-ventricular-wall thickness and increased afterload ($P \leq 0.001$).

Conclusions. Female sex and a higher rate of administration of doxorubicin were independent risk factors for cardiac abnormalities after treatment with doxorubicin for childhood cancer; the prevalence and severity of abnormalities increased with longer follow-up. (N Engl J Med 1995;332:1738-43.)

THERE are more than 150,000 survivors of childhood cancer in the United States,¹ a group that is steadily increasing. By the year 2010, 1 of every 250 adults from 15 to 45 years of age in this country may be a survivor of childhood cancer.¹ Children with common cancers, including sarcomas, and some children with acute lymphoblastic leukemia are frequently treated with the anthracycline doxorubicin.² Anthracyclines improve survival of children with cancer,^{3,4} but at the expense of cardiotoxicity that is related to the cumulative dose of these drugs.⁵ Accordingly, for the past 16 years, treatment protocols have limited cumulative doses, with the result that congestive heart failure during therapy for the initial episode of disease has been rare (<1 percent of patients in some studies).^{2,6,7} Cardiac abnormalities have recently been noted to occur years after treatment, however.⁸⁻¹⁵ In an earlier study, we found that 65 percent of survivors of acute lymphoblastic leukemia in childhood had progressive cardiac abnormalities six years after completing doxorubicin therapy.¹⁰ Late-onset congestive heart failure, symptomatic arrhythmias, and even sudden death have been noted

and are independent of whether congestive heart failure occurred during therapy.⁸⁻¹⁵

Previously, we found that the cumulative dose of doxorubicin was inversely related to left ventricular contractility, and the age at diagnosis was inversely related to afterload.¹⁰ Unfortunately, other potentially influential factors, such as sex and the rate of administration (dosage) of doxorubicin, could not be evaluated at that time. We have now extended that study by evaluating long-term survivors of either acute lymphoblastic leukemia or osteogenic sarcoma, increasing the study population, and broadening the range of dosages and ages at diagnosis. We examined the relations among sex, dosage, cumulative dose, type of cancer, age at the diagnosis of cancer, and length of follow-up, and the associations of these variables with left ventricular function, loading conditions, and contractility.

METHODS

Study Population

We studied 120 children and adults who had been treated with bolus doses of doxorubicin in childhood (87 for acute lymphoblastic leukemia and 33 for nonmetastatic osteogenic sarcoma). All the patients had received their last dose of doxorubicin more than two years previously and had received cumulative doses of at least 244 mg per square meter of body-surface area. We included only patients who had undergone echocardiographic evaluation two years or more after treatment. No patient was known to have had heart disease before receiving doxorubicin or to have received mediastinal or spinal radiation or chemotherapeutic agents other than doxorubicin that are known to be associated with chronic or late cardiotoxic effects. No patient had known anemia or hypothyroidism at the time of the echocardiographic evaluation. This study was approved by the committees on human investigation at Children's Hospital and the Dana-Farber Cancer Institute.

Between 1972 and 1987, children with acute lymphoblastic leukemia were treated according to one of five protocols that included dox-

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orubicin at a dose of 30 mg per square meter or 45 to 60 mg per square meter every three weeks.^{12,16} Patients were eligible for the current study if they had entered complete remission and had not relapsed at the time of the echocardiographic evaluation. Eighty-seven patients (50 percent of those who met the eligibility criteria) agreed to participate and underwent echocardiographic evaluation adequate to meet the requirements of the study; these 87 are a subgroup of the 115 patients described in our previous report.¹⁰ Of this group, 59 received doxorubicin at a dose of 30 mg per square meter every three weeks, and 28 received 45 to 60 mg per square meter every three weeks.

Patients with osteogenic sarcoma were treated according to one of six protocols, all of which included the administration of boluses of doxorubicin. Twenty patients were treated with 75 mg of doxorubicin per square meter every three weeks, eight patients with 75 mg of doxorubicin per square meter in combination with cisplatin every three weeks, and five patients with four doses of 50 mg of doxorubicin per square meter followed by two doses of 90 mg per square meter every three weeks.¹⁷⁻¹⁹ Thirty-three patients with osteogenic sarcoma (51 percent of the eligible patients) participated in this study.

Echocardiographic Evaluation

Echocardiograms were analyzed by cardiologists who were unaware of each patient's treatment protocol, cumulative dose of doxorubicin, and dosage. The echocardiographic study consisted of a complete two-dimensional echocardiogram and Doppler evaluation with stress-velocity analysis, as reported previously.²⁰

For comparison, we used data from 296 normal subjects less than 44 years of age who had been studied in our echocardiography laboratory according to the same protocol.²⁰ Although we found no association between sex and measures of cardiac function (data not shown), others have described sex-related differences in cardiac measurements in a normal adult population.²¹ Therefore, we used sex-specific standardized scores or z scores (expressed as the number of standard deviations above or below the value for the normal controls) for each cardiac measurement in this study in order to control for variations in age, sex, and body size. We determined age- and sex-specific normal ranges for fractional shortening, contractility (measured as the stress-velocity index), and afterload (measured as end-systolic wall stress) and used these data to calculate z scores for the study group. We obtained z scores according to body-surface area and sex for left ventricular end-diastolic dimension, end-diastolic posterior-wall thickness, and mass.

Statistical Analysis

We evaluated the potential effects of sex, age at the diagnosis of cancer, the cumulative dose of doxorubicin, the doxorubicin dosage, the length of time since the completion of therapy, and the oncologic diagnosis on cardiac status. In univariate analyses, we used a two-sample t-test for dichotomous variables and simple linear regression for continuous variables. In multivariate analyses, we used linear regression to examine the relation between measures of cardiac function and possible predictive variables. We used a step-down procedure to identify important predictors for each outcome variable. That is, we started with all the potential predictive factors and dropped the least significant, one at a time. Predictors were kept in the model if the P value was less than 0.05 (the analysis was performed with SAS Proc Reg Software). We assessed potential interactions between predictive factors if there was a biologic justification for doing so. However, because patients with leukemia received doses of 60 mg or less of doxorubicin per square meter and patients with osteogenic sarcoma generally received doses of 75 mg or more per square meter, we were unable to examine the relations of both disease and dosage to cardiac outcome. Although the effect of sex on cardiac status was hypothesized a priori,²² the other predictors were examined in an exploratory way. Since we did not adjust the P values for multiple testing, they should be interpreted cautiously. All P values are two-tailed.

RESULTS

Study Population

The characteristics of the study patients and their treatments are summarized according to diagnosis and

sex in Table 1. The base-line characteristics of the eligible nonparticipating subjects and the participants were similar (data not shown). No clinical cardiotoxic effects were observed in nonparticipants, regardless of sex, suggesting that our results were not biased because of an imbalance of male or female patients with cardiotoxic effects who did not participate.

Twelve study patients had had transient early congestive heart failure during or within one year after completing doxorubicin treatment. Congestive heart failure occurred later in 12 study patients, 7 of whom had also had early congestive heart failure 3 to 16 years previously. In 3 of these 12 patients with late congestive heart failure, medical treatment failed; one underwent heart transplantation, one underwent heart-lung transplantation, and one died from documented ventricular fibrillation. Five of these 12 patients had initial episodes of congestive heart failure a mean of 10.2 years after completing doxorubicin treatment, including 2 women during the peripartum period and 1 patient during nonanthracycline chemotherapy for a relapse of cancer. When patients with clinical evidence of cardiotoxicity were excluded, the results were similar (data not shown).

Results of Echocardiography

In the entire study cohort, the mean z scores for all echocardiographic end points two or more years after the completion of therapy were significantly abnormal. However, stratification according to sex revealed that the increased left ventricular dimension, reduced left ventricular mass, and reduced systolic blood pressure in the cohort were due primarily to abnormalities in fe-

Table 1. Characteristics of the Patients According to Oncologic Diagnosis and Sex.

CHARACTERISTIC	ACUTE LYMPHOBLASTIC LEUKEMIA	OSTEOGENIC SARCOMA	FEMALE PATIENTS*	MALE PATIENTS*
No. of patients	87	33	62	58
Percentage of eligible patients enrolled	50	51	52	48
Sex (M/F)	40/47	18/15	—	—
Cumulative dose of doxorubicin (mg/m ²)				
Median	395	390	419	380
Range	244-550	263-450	244-550	248-516
Doxorubicin dosage (mg/m ² /3 wk)	30-60	75-90†	—	—
Age at diagnosis (yr)				
Median	4.8	14.0	6.3	7.5
Range	0.6-19.0	2.8-28.9	0.6-23.9	1.3-28.9
Time since completion of therapy (yr)				
Median	8.1	8.1	8.6	7.3
Range	2.0-14.6	2.0-13.7	2.0-14.6	2.0-14.4
Age at time of study (yr)				
Median	14.2	23.4	15.7	15.7
Range	4.6-31.7	11.0-36.9	4.6-16.9	6.2-33.1

*There were no significant differences between the sexes in these variables ($P > 0.35$ by the Wilcoxon rank-sum test).

†Five patients received four doses of 50 mg of doxorubicin per square meter, followed by two doses of 90 mg per square meter. These patients have been analyzed as having received doxorubicin at doses of 75 mg per square meter. There were no significant differences in the results when these patients were analyzed as having received 90 mg of doxorubicin per square meter.

male patients (Table 2). Reduced left ventricular contractility, wall thickness, and fractional shortening, as well as increased left ventricular afterload, were noted in both male and female patients. Peak wall stress was also significantly elevated, indicating an inadequate amount of left ventricular mass. Forty-five percent of the female patients (28 of 62) had depressed contractility (more than 2 SD below the normal value), as compared with 12 percent of the male patients (7 of 58; $P < 0.001$).

Predictors of Cardiac Abnormalities

Univariate analyses revealed relations similar to those shown by the multivariate analyses and are not reported here. Table 3 shows the relation between potential risk factors and the occurrence of cardiac abnormalities in the multivariate analyses, described in detail below.

Sex

For both diseases, female patients had a significantly greater reduction in contractility than did male patients. However, the relation between sex and the cumulative dose of doxorubicin was interactive; the higher the cumulative dose, the greater the difference in contractility between female and male patients (Fig. 1).

As Table 3 shows, female patients had significantly lower left ventricular mass than male patients. Although left ventricular mass was decreased in patients of both sexes, the decrease was significant only for female patients (Table 2).

Doxorubicin Dosage

Higher-dose regimens of doxorubicin were strongly associated with increased afterload and decreased fractional shortening. The reduction in ventricular function was proportional to, and therefore explained by, the increase in afterload; this relation was reflected by the fact that contractility was not related to the rate at which doxorubicin was administered. Higher-dose reg-

Table 3. Relations between Noncardiac Risk Factors and Cardiac Findings in the Multivariate Analyses, According to Oncologic Diagnosis.

CARDIAC MEASURE AND RISK FACTOR	NO. OF PATIENTS*	ACUTE LYMPHOBLASTIC LEUKEMIA		OSTEOGENIC SARCOMA		R ² †
		ESTIMATED CHANGE IN SD‡	P VALUE	ESTIMATED CHANGE IN SD‡	P VALUE	
Contractility	120					0.65
Female sex§		-0.0028 ×dose¶	<0.001	-0.0028 ×dose¶	<0.001	
Mass	114					0.08
Female sex		-0.1439	0.62	-0.8328	0.05	
Age at diagnosis§		0.0661	0.007	0.0661	0.007	
Wall thickness	117					0.11
Age at diagnosis§		0.0580	0.02	0.0580	0.02	
Years since completion of therapy§		-0.1200	0.004	-0.1200	0.004	
Dimension	118					0.07
Dosage		0.0407	0.009	0.0145	0.06	
Afterload	115					0.35
Dosage		0.1117	<0.001	0.0558	<0.001	
Age at diagnosis§		-0.1212	0.006	-0.1212	0.006	
Years since completion of therapy§		0.3001	<0.001	0.3001	<0.001	
Fractional shortening	115					0.28
Age at diagnosis§		0.0876	0.02	0.0876	0.02	
Dosage		-0.0543	0.02	0.0380	0.001	
Cumulative dose§		-0.0146	<0.001	-0.0146	<0.001	

*Data were missing for some variables used in the models, so not all regressions included data on all 120 patients.

†The coefficient of determination — that is, the proportion of the variation in the response explained by the covariates.

‡Beta coefficient from the multiple regression indicating the change in the standard deviation for the cardiac measure that is predicted by a one-unit change in the risk factor.

§The effects of this risk factor on the variable in question were found to be similar for patients with acute lymphoblastic leukemia and those with osteogenic sarcoma, so a single estimate of the effect is reported for both groups.

¶There was an interaction between sex and cumulative dose, so that the effect of sex depends on the dose. The factor shown multiplied by the cumulative dose of doxorubicin in milligrams per square meter results in the estimated value.

imens of doxorubicin were also associated with increased left ventricular end-diastolic dimension.

Cumulative Dose of Doxorubicin

In addition to the sex-specific effect of higher cumulative doxorubicin doses on left ventricular contractility, higher cumulative doses were associated with reduced fractional shortening. The latter effect could be explained by the reduced contractility, since there was no association between cumulative dose and afterload.

Age at Diagnosis

A younger age at the time of diagnosis was associated with a significantly thinner than normal left ventricular posterior wall at end-diastole and with reduced left ventricular mass. Younger age was also an important predictor of excess left ventricular afterload. As with the doxorubicin dosage, the increased afterload in pa-

Table 2. Echocardiographic Measurements According to Sex.

MEASURE	FEMALE PATIENTS				MALE PATIENTS			
	Z SCORE (P VALUE)*	RAW VALUES†		Z SCORE (P VALUE)*	RAW VALUES†			
		mean	expected		mean	expected		
Contractility (stress-velocity index)	-2.06 (<0.001)	—	—	-0.93 (<0.001)	—	—		
Mass (g)	-0.81 (<0.001)	105	121	-0.36 (0.086)	135	143		
End-diastolic posterior-wall thickness (cm)	-1.79 (<0.001)	0.66	0.81	-1.24 (<0.001)	0.74	0.86		
End-diastolic dimension (cm)	0.62 (0.001)	4.60	4.44	0.11 (0.542)	4.73	4.70		
Afterload (g/cm ²)‡	2.64 (<0.001)	65.9	44.3	2.86 (<0.001)	69	46		
Fractional shortening (%)	-2.10 (<0.001)	28.4	33.8	-1.96 (<0.001)	28.6	33.6		
Systolic blood pressure (mm Hg)	-0.83 (0.002)	97.5	106.7	-0.34 (0.221)	107.6	111.2		
Peak wall stress (g/cm ²)	1.29 (0.071)	163	136	0.60 (0.140)	150	139		

*Z scores are the number of standard deviations above or below the value for normal controls, and the P values are for the comparison with the normal controls (by t-test).

†Measured as the end-systolic wall stress.

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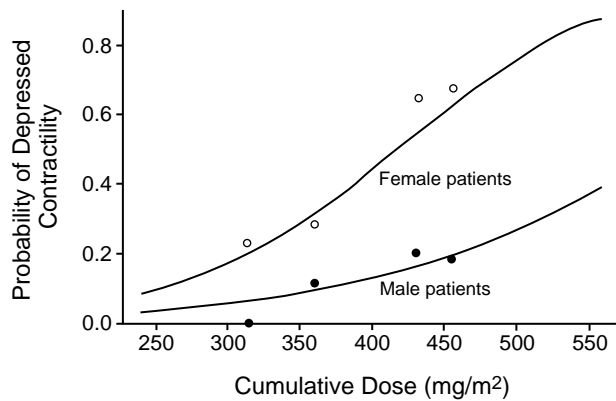


Figure 1. Probability of Depressed Contractility as a Function of the Cumulative Dose of Doxorubicin in Female and Male Patients.

To produce this plot, we formed a dichotomous response variable that equaled 1 if the z score for contractility (measured as the stress-velocity index) was extreme (less than -2) and 0 if it was not (-2 or more). A logistic-regression model was then fitted to the interrelation between female sex and the cumulative dose of doxorubicin (the risk factors) and abnormal left ventricular contractility (the outcome variable). Although the risk was higher for female patients at all cumulative doses, the difference in risk between female and male patients was greater at the higher cumulative doses. The observed proportions of female and male patients with late depressed contractility at four different ranges of the cumulative doxorubicin dose are superimposed on the logistic-regression curves. The four dose groups were formed by grouping patients into quartiles according to cumulative dose and plotting the median dose in each quartile (shown as open and solid circles).

tients who were younger at the time of diagnosis accounted for the significantly diminished fractional shortening.

Years since Doxorubicin Therapy

Patients with longer follow-up periods since the completion of therapy were more likely to have reduced left-ventricular-wall thickness and secondary increases in left ventricular afterload.

Oncologic Diagnosis

The effects of sex and doxorubicin treatment on left ventricular dimension, mass, and fractional shortening appeared to vary with the oncologic diagnosis. Because the age at diagnosis and the dosage were different for the two diseases, however, we could not determine whether the differences in the echocardiographic findings were due to the disease, the dosage, or the age at the initiation of doxorubicin treatment. For other cardiac abnormalities, the relations appeared to be the same for both diseases.

DISCUSSION

Among patients treated with doxorubicin for cancer during childhood, female sex and a higher-dose doxorubicin regimen were independent risk factors for abnormalities of cardiac mechanics and were also independent of the cumulative dose and age at the time of therapy, which have previously been shown to be risk factors for cardiac abnormalities.¹⁰ Both the prevalence and the severity of abnormalities of cardiac growth and

mechanics increased with longer follow-up. The risk factors for abnormal contractility (sex and cumulative dose) were different from those for reduced wall thickness and mass (dosage, age at the time of therapy, time since the completion of treatment, and oncologic diagnosis), suggesting separate mechanisms for these two types of toxicity.

Sex

Female patients appear to be more vulnerable to the adverse effects of treatment of childhood cancer, and male patients may need more intensive treatment than female patients to achieve a similar rate of cure.²³ Girls treated for childhood leukemia²⁴ or other types of cancer²⁵⁻²⁷ are more likely to remain in remission than boys. However, they also appear to have more cardiotoxic effects.^{2,28-31} Our preliminary work suggested that most doxorubicin-treated survivors of childhood leukemia who had late depressed contractility were female²² and that female patients have nearly twice as high a risk of early clinical cardiotoxicity as male patients.² Two recent studies of children demonstrated more abnormalities on exercise testing and nuclear angiography at rest and during exercise in girls than in boys during and after chemotherapy that included anthracyclines.^{30,31} These findings are difficult to interpret, however, since similar sex-related differences in the cardiac responses of supine patients to exercise, as assessed by radionuclide angiography, have also been documented in normal persons.³²

We do not understand why doxorubicin affects left ventricular contractility more profoundly in female patients than in male patients. Possible mechanisms include differences in oxidative stress, differential expression of the multidrug-resistance gene, and body composition.

Differences in body composition between girls and boys^{33,34} could influence drug toxicity by altering the metabolism or the volume of distribution of doxorubicin. Doxorubicin does not reach a high concentration in fat,³⁵⁻³⁷ and its clearance is reduced with increased body fat.³⁷ Consequently, if girls have more body fat than boys with the same body-surface area, equivalent doses of doxorubicin could lead to higher concentrations, for a longer time, in nonadipose tissue (including the heart) in girls.

Prednisone therapy also increases the percentage of body fat. The children treated for leukemia also received prednisone and appeared to have more late cardiac abnormalities than those treated for osteogenic sarcoma, who did not receive prednisone. That prednisone therapy increases the risk of subsequent cardiotoxic effects of doxorubicin by increasing the percentage of body fat is a hypothesis that should be tested.

Dose of Doxorubicin

Most treatment programs establish upper limits for cumulative doses of doxorubicin that result in less depressed contractility during treatment; however, many protocols for childhood cancers include intensified therapy, with high dose rates.^{4,17-19} Our findings suggest

that even when the cumulative dose is limited, higher dose rates are an important predictor of increased afterload and depressed left ventricular function years after treatment. Presumably, higher bolus doses produce higher levels of doxorubicin in blood and tissue that affect subsequent left ventricular mass and result in the increased afterload and depressed left ventricular function that we observed.

Age at Diagnosis and Time since Doxorubicin Therapy

Patients who were younger at the time of diagnosis had the greatest reductions in left ventricular mass and the most profound increases in afterload. As we have previously suggested,¹⁰ this difference could be due to the inhibition of myocardial growth by doxorubicin, which would be accentuated in younger children, whose left ventricular mass is smaller. Perhaps higher levels of doxorubicin in tissue and blood occurred in younger patients because of their higher percentage of body fat.^{33,34}

Because time is required for somatic growth to outstrip myocardial growth, the myocardial effects of doxorubicin on left ventricular mass and afterload become more obvious over time, and progressive cardiac abnormalities may occur. The effect of the length of follow-up and of sex on cardiac growth and function may be clinically apparent only after prolonged observation. For example, female survivors of childhood cancer were less likely to die than male survivors if the disease was diagnosed when they were between 12 and 20 years old; before 12 years of age, there was no difference.³⁸ Among patients in whom cancer was diagnosed during adolescence, Byrne et al. found that the survival advantage of female patients extended beyond the immediate treatment period but diminished with increasing follow-up and was no longer significant beyond 30 years of age.³⁸ We do not know how many patients in that series were treated with anthracyclines. However, if the study group was representative of groups studied in pediatric oncology protocols in the United States,² the effect of sex on late cardiotoxicity may have a role in the eventual neutralization of the survival advantage among female patients treated for cancer during adolescence and may contribute to the lack of a survival advantage among girls treated before 12 years of age. Female sex has also been associated with a higher risk of potentially life-threatening cardiac arrhythmias after drug treatment for cardiovascular disease, a fact that may also contribute to the reduction of the survival advantage in female patients with time.³⁹ The prognosis after myocardial damage from infarction or congestive heart failure is probably worse for women, among whom higher mortality rates have been observed than among men,⁴⁰ again suggesting that substantial myocardial damage after treatment with doxorubicin may reduce survival more in women.

In conclusion, limiting the cumulative dose of doxorubicin may not suffice to prevent late cardiotoxic effects in patients treated for cancer during childhood. At a minimum, sex and the dosage of doxorubicin should

also be considered when treatment protocols are designed. For the many current survivors of childhood cancer who received bolus doses of anthracyclines, careful evaluation is necessary to detect subclinical cardiac abnormalities. Girls who were treated with high cumulative doses of anthracyclines or with regimens of high individual doses, as well as patients of both sexes who were relatively young at the time of treatment or have had long periods of follow-up since doxorubicin therapy, appear to be at the highest risk for late cardiotoxic effects.

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