Late Cardiotoxic Effects of Anthracycline Chemotherapy in Childhood Malignancies

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Abstract

Objective: To determine the frequency of changes in left ventricular function in patients, at least 5 years after completion of anthracycline-therapy for childhood malignancy.

Methods: Echocardiographic examination was performed on 58 patients (36 males and 22 females) with mean age of 17.5±4.6 years (range 9-29 years, median 17.5 years). The control group was 58 healthy age and sex matched children.

Results: The age at the time of diagnosis and start of treatment ranged from 2 to 14 years with a median of 6 years. The time of follow-up was between 5 to 22 years with a median of 9 years. The cumulative dose of anthracycline was 30 to 557 mg/m^2, median 128.5 mg/m^2. All the patients were asymptomatic. Abnormal systolic and/or diastolic functions were found in 29 (50%) patients. We found a strong correlation between systolic and diastolic cardiac dysfunction and longer time of follow-up ($P = 0.02$ and $p = 0.04$), respectively, but not a relation to the cumulative dose, sex, and age at diagnosis.

Conclusion: The data showed a relatively high incidence of subclinical cardiotoxicity in long-term survivors. The significance of this subclinical cardiotoxicity on the morbidity and mortality of patients should be followed in the future (JPMA 58:683; 2008).

Introduction

Anthracycline cardiomyopathy is an increasingly common problem among children and young adults in view of the high survival rates now achieved for childhood malignancies treated with anthracycline containing regimens.[1] A rapidly growing number of persons, including an alarming fraction of the adults who have survived childhood cancer will have substantial morbidity and mortality because of anthracycline - related cardiac disease.[2] Kremer et al reviewed all studies published between 1966 and 2001 that included more than 50 children with anthracycline cardiotoxicity. The reported frequency of sub clinical cardiotoxicity varied between 0% to 57% in the 25 studies.[3] Larussi et al evaluated 31 survivors of Hodgkins disease and detected abnormal myocardial performance index in 83% of cases.[4] Preliminary data from anthracycline- treated survivors of leukaemia suggest that features of restrictive cardiomyopathy may appear on long-term follow-up.[2] Most late-onset clinical decompensations occur after more than 10 years of follow-up and data from beyond that time point are limited.[2] The incidence of late-onset cardiac decompensation increases with larger cumulative doses,[5-7] mediastinal radiotherapy,[6] female sex,[8] longer duration of follow-up,[6,8] younger age at diagnosis,[9] and malnutrition.[10]

Routine monitoring of all children receiving Adriamycin is required to avoid the mortality and morbidity of Adriamycin-related cardiotoxicity, which may develop at relatively low cumulative doses also.[11] Clinical monitoring of patients based on symptoms and findings of heart failure is not sufficient since time of cardiac contractile dysfunction relative to anthracycline exposure is highly variable and treatable cardiac dysfunction frequently precedes the onset of symptoms. Patients treated with anthracycline need careful cardiac monitoring. This monitoring should be sensitive, non-invasive, and available at reasonable cost.[12] Two-dimensional echocardiography is the primary noninvasive technique used to monitor anthracycline cardiotoxicity, particularly in children. Resting left ventricular ejection fraction (EF) and shortening fraction (SF) are the most commonly used echocardiographic parameters. Parameters of diastolic function have also been examined for their usefulness in detecting early anthracycline-induced cardiac injury.[13] Several reports indicate that stress echocardiography increases the differences in cardiac variables between healthy population and asymptomatic survivors of childhood cancer.[14-16] In a study by Sung et al abnormalities of diastolic function were common among paediatric oncology patients no matter whether they had received anthracycline treatment or not, but abnormalities of systolic function were specific to anthracycline therapy.[17]

The purpose of this study was to determine the frequency of changes in left ventricular function in patients in long-term remission after treatment with anthracycline for a childhood malignancy. We examined the relations among sex, cumulative dose, age at the diagnosis of cancer and beginning of treatment, length of follow-up, and the association of these variables with left ventricular systolic and diastolic functions.

Patients and Methods

Medical records of patients previously treated in childhood for malignant disease at Paediatric Ward of Shohada Hospital, Iran, were evaluated, and 72 patients were identified as having survival more than 5 years from last exposure to anthracycline drugs. These patients were recalled for cardiovascular assessment and 58 cases who had regular outpatients follow up attended (response rate = 80%). Previous histories were determined from detailed review of case notes. All patients had received other cytotoxic agents; the majority of which are not considered cardiotoxic. The length of follow-up was measured from last exposure to anthracycline. Patients were eligible for the study if they had entered complete remission and had not relapsed at the time of echocardiographic evaluation. The patients had no symptoms of cardiac dysfunction at their last clinical review.

Full cardiovascular examination was performed by a paediatric cardiologist, who was unaware of clinical details. Echocardiographic examinations were performed in the left lateral semi recumbent position. Cross sectional images were taken from the standard parasternal, apical, and subcostal views to confirm the presence of normal cardiac anatomy.Transmitral flow velocity patterns were recorded from the apical four chamber view. M-mode tracings were obtained from the parasternal long axis view. The values of ejection fraction below 55% and fractional shortening below 30% were considered as pathological. A 12-lead ECG was preformed in each patients. Echocardiographic data were compared with those of 58 healthy children and young adults examined by identical techniques.

The study was approved by the Ethical Review Board of the Institution.

The risk factors that were evaluated included sex, age at diagnosis, total dose of anthracycline, and duration of follow-up since completion of therapy. Echocardiographic data of cases and controls were compared by t-test. Correlation between cardiac indices and risk factors were measured by Pearson correlation test. The relationship between sex and cardiac indices were evaluated by Chi-Square test. The correlation between several risk factors with cardiac parameters were evaluated by stepwise multiple linear regression analysis. Probability values of <0.05 were considered statistically significant.

Results

During the study period (March to September 2005) fifty-eight consecutive asymptomatic patients attending the outpatient clinic of paediatric haematology-oncology, for follow-up, were referred for echocardiographic examination. None of them had clinical signs and symptom of cardiac decompensation. The time past from the last anthracycline dose was at least 5 years or more for all of them. The patients comprised 36 (62.1%) males and 22 (37.9%) females aged 17.5±4.6 years (range 9-29 years, median 17.5 years). The age at the time of diagnosis and start of treatment was 6.9±3.3 years (range 2-14 years, median 6 years). The time of follow-up was 10.7±4.6 years (range 5-22 years, median 9 years). The patients were given

Table 1: Oncologic profile of patients.

Variable — Frequency	N (%)
Type of malignancy	
ALL	28 (48.3)
Hodgkin disease	12 (20.7)
Willms'tumor	6 (10.3)
Lymphoma, Burkitt lymphoma	5 (8.6)
Miscellaneous	7 (12.1)
Type of drug	
Adriamycin	31 (52.6)
Daunomycin	27 (47.4)
Cumulative dose	
< 100 mg/m2	18 (31)
100 - 300 mg/m2	32 (55.2)
> 300 mg/m2	8 (13.8)
Age at diagnosis	
< 5 years	15 (25.9)
5-10 years	32 (55.2)
> 10 years	11 (18.9)
Duration of follow-up	
5 - 10 years	35 (60.3)
11 -15 years	15 (25.9)
> 15 years	8 (13.8)

Table 2: Systolic function of patients and controls.

Parameter	Patients mean ± SD (n = 58)	Controls mean ± SD (n = 58)	P Value
SF (%)	33.3 ± 3.7	37 ± 3.2	0.001
EF (%)	62.5 ± 5.2	67.4 ± 4.1	0.001
LVEDD (mm)	3.82 ± 0.55	3.89 ± 0.5	0.5
LVESD (mm)	2.55 ± 0.39	2.44 ± 0.37	0.1
PW (mm)	1.05 ± 0.18	1.09 ± 0.22	0.4
IVS (mm)	1.06 ± 0.21	1.15 ± 0.21	0.03

SF = shortening fraction, EF = ejection fraction, LVEDD = left ventricular end diastolic diameter, LVESD = left ventricular end systolic diameter, PW = posterior wall, IVS = inter ventricular septum.

Table 3: Diastolic function of patients and controls.

Parameter	Patients mean ± SD (n = 58)	Controls mean ± SD (n = 58)	P Value
E (cm/sec)	94.5 ± 19.7	84.6 ± 9.9	0.001
A (cm/sec)	46.3 ± 12.8	50.5 ± 9.2	0.04
E/A ratio	2.1 ± 0.43	1.67 ± 0.16	0.001
EF Slope (cm/sec)	4.6 ± 1.2	4.1 ± 0.8	0.02
DT (msec)	111.64 ± 25.3	170.01 ± 25.5	0.001
IVRT (msec)	71.3 ± 17.1	84.4 ± 9.6	0.001

E = peak flow velocity in early diastole, A = peak flow velocity during atrial contraction, EF slope = rate of deceleration of flow velocity in early diastole, DT = deceleration time, IVRT = isovolumic relaxation time.

a cumulative dose of doxorubicin or daunomycin of 176.1±128 mg/m^2 (range 30-557 mg/m^2, median 128.5mg/m^2).

The control group consisted of 36 males and 22 females aged 16.5±5.1 years (range 6-28 years, median 17 years). Regarding the age there was no significant difference between cases and controls (p=0.5). Table 1 shows the oncologic profile of patients. Twenty - eight (48.3%) suffered from acute lymphoblastic leukemia, whereas 30 (51.7%) had different types of solid tumors. The majority of patients did not receive radiation and did not experience relapses. A minority of them (13.8%) received cumulative doses more than 300 mg/m^2 and 39.7% had more than 10 years of follow-up.

Cardiac evaluation included a complete physical examination, chest x-ray, 12 lead ECG, and echocardiography. Systolic and diastolic blood pressures were within normal limits for all patients. All the cases had normal chest x-ray. The ECG did not show dysrhythmia. Sinus tachycardia (heart rate ≥ 100/min) was noted in 16 (27.6%) patients.

Table 2 compares the systolic parameters, measured by M-mode echocardiography, in cases and controls. Nine (15.5%) patients had shortening fraction (SF) less than 30% and one of them had ejection fraction (EF) less than 55%. SF and EF in patients were less than those in controls and the differences were significant (p=0.001, p=0.001 respectively). SF and EF in patients with heart rate ≥ 100/min were less than those in patients with heart rate < 100/min and the differences were significant (31.1±3.4 versus 34.1±3.5, p = 0.006 and 59.7±5.2 versus 63.6±4.8 , p = 0.02 respectively).

Table 3 compares the diastolic parameters, measured by 2-D echocardiography, in cases and controls. Peak flow velocity in early diastole (E wave), rate of flow velocity after the early diastolic peak (EF slope), and the ratio between the early and late peaks of flow velocity (E/A) were increased in patients compared to those in controls and the differences were significant (p = 0.001, p = 0.02, p = 0.001 respectively). The flow velocity deceleration time (DT) and isovolumic relaxation time (IVRT) were decreased in patients compared to those in controls and the differences were significant (p = 0.001, p = 0.001 respectively). Twenty - nine (50%) cases showed one or more diastolic parameter abnormalities and nine of them had systolic dysfunction in addition to diastolic dysfunction.

We compared the relationship between oncologic factors and systolic/diastolic cardiac function parameters in patients. Regression analysis showed that the SF, EF, and deceleration time were inversely correlated with duration of follow-up (p = 0.02, and p = 0.04 respectively). There was no relationship between cardiac function parameters and sex, cumulative dose of anthracycline, and age of diagnosis.

Discussion

In our study 16 cases developed sinus tachycardia and SF was inversely proportional to heart rate (p=0.02). Sinus tachycardia is the most common rhythm disturbances in theses patients.[12] In a previous report by Bu' Lock et al, patients with SF<30% had a much faster heart rate than those with SF ≥ 30%.[6] Steinherz and associates who studied the clinical course of late symptomatic anthracycline cardiomyopathy found conduction abnormalities in 14/15 patients.[18] In a study by Tjeerdsma et al, 24 hour Holter monitoring showed abnormal heart rate variability in 85% of patients.[19]

Our data indicated that the thickness of interventricular septum in cases were significantly less than those in controls (p=0.03). Larussi and associates reported that in childhood, reduced myocardial thickness and increased afterload explains much of systolic and diastolic dysfunction of late anthracycline toxicity.[20] In a previous research by Lipshultz et al,[7] 115 doxorubicin-treated long-term survivors of childhood acute lymphoblastic leukaemia (median follow-up after completion of therapy was 11.8

years) had been studied. Left ventricular fractional shortening was significantly reduced after doxorubicin therapy. Reduced fractional shortening was related to impaired contractility and increasing afterload, consequences of a progressive reduction of ventricular mass, and wall thickness.[7]

The abnormal systolic or diastolic findings were between 8% to 83% in different series.[4,5,9,19,21,22] The early peak flow velocities in our patients were significantly higher than those in controls. Deceleration time and isovolumic relaxation time in our patients were decreased compared with those in controls and the differences were significant. The above findings are compatible with a restrictive pattern of myocardial dysfunction.

Cumulative doses of anthracycline being used are an important risk factor for cardiac toxicity. We did not find a relationship between cumulative doses and cardiac dysfunction. It may be due to wide range (30 mg/m^2 to 557 mg/m^2) of cumulative doses in our cases. In a research by Hauser et al the parameters of cardiac dysfunction were not related to the dosage of administered doxorubicin.[15] It may be due to the fact that cardiac dysfunction in their patients were provoked by stress echocardiography. Investigations showed that asymptomatic children treated with moderate doses of anthracycline for cancer, sustain sub clinical myocardial damage and there is not a safe dose of doxorubicin that was free of late toxicity.[2] The incidence of echocardiographic abnormalities increased with the duration of follow-up.[8,13,18] This finding indicates that the full extent of the problem has yet to be unfolding in many asymptomatic patients after remote anthracycline treatment. Elbl et al[5] who examined 155 patients in long-term remission after treatment with anthracycline for a childhood malignancy did not find a relation between parameters of left ventricular systolic function and time indicators (age at diagnosis, time of follow-up). The median duration of follow-up in their study was 15 years. They opined that further monitoring and evaluation of the relevant subclinical abnormalities over a longer period of time are needed.[5] In a report by Godoy and associates,[9] among 120 children with malignancies who received anthracycline, children younger than 4 years had a higher incidence of cardio toxicity compared with those older than 4 years ($p<0.01$).[9] An investigation by Bu' Lock et al[6] revealed that the relative risk of symptomatic cardiac failure was greatly increased by prior irradiation.[6] Our findings revealed a significant relationship between longer period of follow-up and abnormal systolic or diastolic cardiac function.

Conclusion

Regarding the relatively high incidence of abnormal echocardiographic findings in our patients, we conclude that there is a high frequency of cardio toxicity in our patients in spite of moderately lower doses of anthracycline being used. Most of this cardiotoxicity is subclinical because none of our patients were symptomatic. How this subclinical toxicity will affect future morbidity and mortality is difficult to predict from this data.

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