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Original Research Article

Study of Late Anthracycline Cardiotoxicity in Childhood Cancer Survivors

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Abstract

Background: Anthracyclines are the most commonly used drugs in paediatric cancers. Early and late cardiac side effects are reported with anthracyclines. Children should be followed up into adulthood anticipating the delayed side effects of anthracyclines.

Aims: To evaluate cardiac electrophysiological and functional parameters in long term survivors of childhood malignancy who received anthracycline therapy, using electrocardiogram and echocardiography.

Materials and Methods: This cross-sectional study was conducted by the Department of Medicine and Department of Pediatrics at a tertiary care teaching hospital in Kurnool between Sep 2019 and February 2022. The study group consisted of 25 cases of long-term survivors of childhood malignancy who received anthracycline therapy.

Results: Total 25 patients were divided into 3 groups based on cumulative dose of anthracyclines: <300 mg/m^2, 300 – 400 mg/m^2, >400 mg/m^2. Among 25 patients 19 were treated for ALL, 5 were treated for lymphoma and 1 was treated for Hepatoblastoma. Two relapsed cases of ALL received more than 400mg/m^2 of anthracycline dose. Comparison of electrocardiographic variables (HR; PR interval; QTc interval; QRS axis, amplitude and duration; R/S in V1 and V6) between the groups were not significant. In the three cumulative dose groups there is no statistically significant difference between echocardiographic variables

Keywords: Hepatoblastoma, Anthracycline Dose, Electrocardiographic variables

Background

Cancer is an important cause of mortality in many of the economically developed nations of the world. More than 10% of all deaths in children below 15 years of age are caused by malignant diseases in developed countries. Childhood cancers are unique in the sense that they arise from embryonal cells, respond to treatment rapidly and the survival has improved dramatically over the last two decades due to aggressive combined modality management [1,2].

Due to the significant advances in modern medicine and effective treatment of cancers,today most children diagnosed with malignancy are expected to become long term cancer survivors. As the number

of childhood cancer survivors grows, so too does the need for evidence-based surveillance of long-term effects of cancer therapy.

Cardiotoxicity has been extensively reviewed with the use of anthracyclines, [3,4] which is one of the commonly used drugs in pediatric cancers. Anthracyclines have been reported to cause cardiomyopathy, congestive heart failure and ECG alterations (e.g. nonspecific ST-T changes, decreased QRS voltage and prolongation of QT interval). Both early and late onset cardiac effects are reported. Early onset effects occur within one year after start of the anthracycline therapy and can be acute, sub- acute or chronically progressive. In children early onset cardiotoxicity seems to occur less frequently than late onset clinical cardiotoxicity. Late onset effects can occur up to 20 years after completion of anthracycline therapy [4].

In India too there is a marked improvement in the treatment of childhood cancers and there is an increasing population of childhood cancer survivors. The treatment of childhood cancers does not end with the completion of the formulated protocols. These children should be followed up into their adulthood anticipating the long-term adverse effects of the chemotherapy and radiotherapy, including the delayed cardiotoxicity of anthracyclines.

Aims and Objectives

To evaluate cardiac electrophysiological and functional parameters in long term survivors of childhood malignancy who received anthracycline therapy, using electrocardiogram and echocardiography.

Materials and Methods

This cross-sectional study was conducted by the Department of Medicine and Department of Paediatrics, at a tertiary care teaching hospital in kurnool between September 2019 and February 2022. The study group consisted of 25 cases of long-term survivors of childhood malignancy who received anthracycline therapy.

Inclusion Criteria: Cases of childhood malignancy who had completed chemotherapy (Anthracyclines) by more than 1 year and evaluated earlier for cardiotoxicity during and after chemotherapy.

Exclusion Criteria: Children who had preexisting cardiac disease or problem confirmed by baseline ECG and ECHO before starting anthracycline therapy.

Methodology: Following inclusion into the study, an informed consent was taken. A detailed documentation of symptomatology and clinical features was performed for all patients to ascertain various risk factors for anthracycline cardiotoxicity. Daunorubicin and doxorubicin were considered equivalently cardiotoxic in our study and equivalent dose of doxorubicin was calculated ($60mg/m^2$ daunorubicin is equivalent to $50mg/m^2$ of doxorubicin).

Electrocardiogram: A twelve lead ECG was performed in each patient and following ECG complexes and intervals were evaluated:

Heart rate, PR interval, QTc interval, QRS- Axis, duration and Amplitude (Algebraic sum of 6 limb leads), R/S ratio in V_1, V_6

All electrocardiograms were recorded by one technician to eliminate inter observer variability with measurements being recorded in each case after 10 minutes of bed rest.

Echocardiogram: The position and angulation of the probe was carefully checked before each study. Cross sectional imaging, performed from the standard parasternal-long axis, short axis; apical- 2, 4, 5 chamber planes and sub-costal-4 chamber plane view to confirm for presence of normal cardiac anatomy. Three cardiac cycles were recorded and the cycle with highest velocity, selected for further analysis in order to reduce the

influence of respiration on myocardial velocities (and for the fact that breath holding is not always feasible in young children). An electrocardiographic trace was recorded simultaneously with ECHO, chart speed @ 100mm/sec for all recordings.

M-mode echocardiography was recorded at the tip of mitral valve leaflets at the parasternal long axis view. Diastolic and systolic dimensions of left ventricle were measured using M-mode echocardiography as recommended by American Society of Echocardiology.

Fractional shortening (FS) – was calculated from these as follows:

$$FS = \frac{LVIDd - LVIDs}{LVIDd}$$

LVIDd: Left ventricular diameter in end diastole.

LVIDs: Left ventricular diameter in end systole.

Left ventricular end-systolic (LVSV) and end-diastolic volumes (LVDV) was measured by 2-D echocardiography using modified Simpson's technique.

Ejection fraction (EF) – was calculated from these volumes as follows:

$$EF = \frac{LVDV - LVSV}{LVDV}$$

Following these, the cursor was then placed at the mitral valve orifice. The position of sample volume to be taken at the point where there is highest early mitral velocity. The mitral peak early (E wave, onset of early diastole) and peak atrial (A wave, onset of late diastole) velocities was measured to calculate mitral valve E/A ratio.

Myocardial performance index (MPI)

It is defined as the sum of isovolumic relaxation (IVRT) divided by ventricular ejection time. To obtain the sum of isovolumic contraction time (ICT) and IVRT, the left ventricular ejection time subtracted from the interval from cessation to onset of mitral valve inflow. The difference is then divided by ejection time to derive MPI for left ventricle.

The mitral inflow velocity was recorded from the apical 4-chamber or apical long-axis view with the pulsed-wave Doppler. The sample volume was positioned at the tips of the mitral leaflets during diastole (to record 'a'). Subsequently, the left ventricular outflow velocity pattern was recorded from the apical long-axis view with the Doppler sample volume positioning just below the aortic valve (to record 'b').

Cardiac dysfunction was defined as ejection fraction <56%, fractional shortening <29% (as per guidelines of Cardiology Committee of the Children Cancer Study Group) and myocardial performance index <0.34.

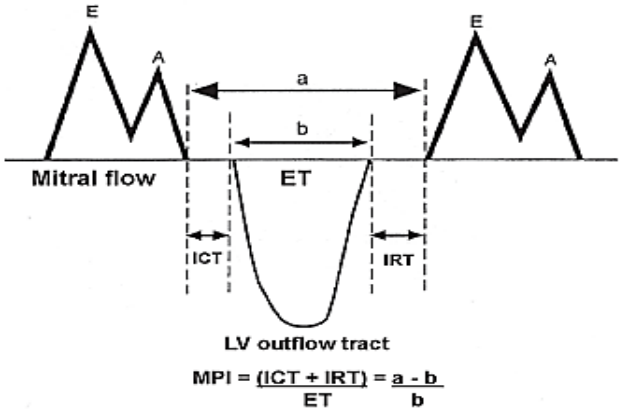

Figure 1: Schema for measurements of Doppler time interval – Myocardial performance index

Cardiac dysfunction was defined as ejection fraction <56%, fractional shortening <29% (as per guidelines of Cardiology Committee of the Children Cancer Study Group) and myocardial performance index <0.34.

All 25 cases were divided into 3 groups based on cumulative anthracycline dose. These 3 groups were compared using Kruskal Wallis test. All the data was analyzed by SPSS (statistical package foe social science) 20.0 version.

Results and Analysis

A total of 25 patients were enrolled for the study. They were treated for childhood malignancy with the chemotherapeutic drugs including anthracyclines and monitored for cardiac dysfunction during chemotherapy. Among 25 patients 19 were treated for ALL, 5 were treated for lymphoma and 1 was treated for Hepatoblastoma. Two relapsed cases of ALL received more than 400mg/m^2 of anthracycline dose.

Total patients divided into 3 groups based on cumulative dose of anthracyclines: <300 mg/m^2, 300 – 400 mg/m^2, >400 mg/m^2.

Mean age at diagnosis of malignancy was 7years 4 months. Mean duration after completion of treatment was 5 years 6 months.

Sex distribution

Table 1: Sex distribution

Sex	Total	%
Male	15	60
Female	10	40

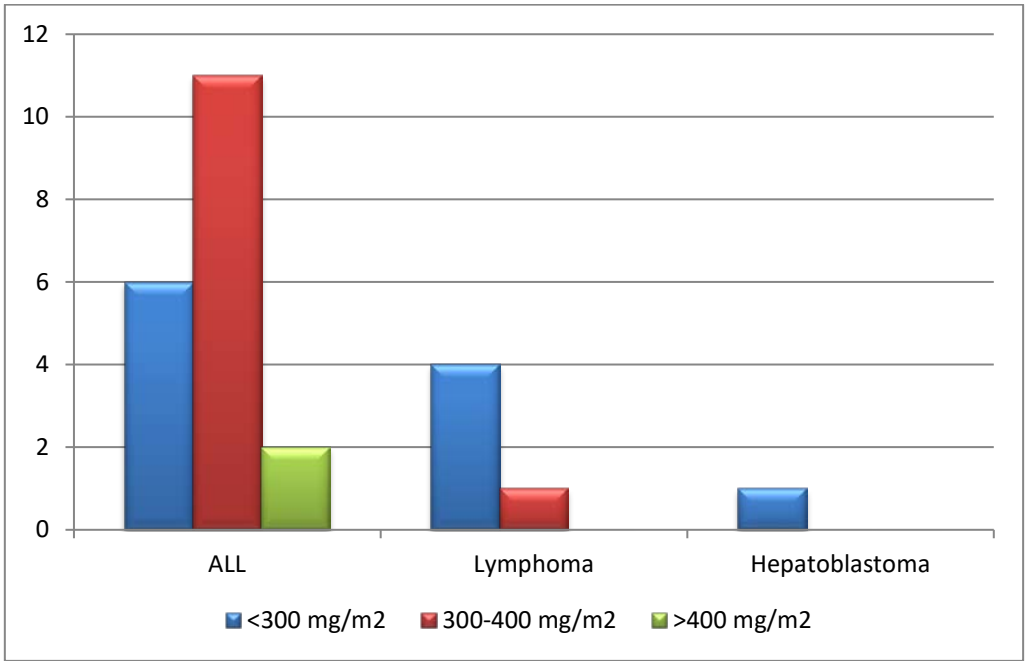

Figure 2: Distribution of diagnosis in various dosage groups

Cumulative anthracycline dose	ALL	Lymphoma	Hepatoblastoma
<300 mg/m^2	6	4	1
300 – 400 mg/m^2	11	1	0
>400 mg/m^2	2	0	0

Electrocardiogram variables in each group:

Comparison of electrocardiographic variables (HR; PR interval; QTc interval; QRS axis, amplitude and duration; R/S in V1 and V6) between the groups were not significant. Among 25 patients 3 were having abnormal heart rate with 2 having sinus bradycardia and 1 having sinus tachycardia, however it is statistically insignificant.

Table 2: Comparison of electrocardiographic variables

ECG variable	Cumulative anthracycline dose mg/m^2	Mean	Standard deviation	P value
HR	<300	87.36364	17.591320	0.690 NS
	300 - 400	84.41667	19.970243	
	>400	74.00000	19.798990	
PR Interval	<300	0.12909	0.018684	0.275 NS
	300 - 400	0.12333	0.011547	
	>400	0.11000	0.014142	
QTc Interval	<300	0.40909	0.053936	0.451 NS
	300 - 400	0.39417	0.052649	
	>400	0.35000	0.070711	
QRS Duration	<300	0.08000	0.000000	0.540 NS
	300 - 400	0.08000	0.020889	
	>400	0.08000	0.000000	
QRS Axis	<300	75.72727	4.496463	0.673 NS
	300 - 400	77.08333	7.153617	
	>400	74.50000	10.606602	
QRS Amplitude	<300	26.09091	11.536503	0.601 NS
	300 - 400	26.25000	5.172040	
	>400	23.50000	2.121320	
R/S in V1	<300	0.53818	0.273416	0.572 NS
	300 - 400	0.47333	0.188696	
	>400	1.03000	0.890955	
R/S in V6	<300	10.81818	6.341422	0.450 NS
	300 - 400	10.04167	5.698717	
	>400	5.10000	5.515433	

NS: Not significant

Echocardiographic variables in each group:

1. EF, FS and MPI were assessed in all 25 children and analyzed according to the cumulative dosage groups.
2. In the three cumulative dose groups there is no statistically significant difference between echocardiographic variables.

Table 3: Echocardiographic variables in various dosage groups

Echocardiographic variable	Cumulative anthracycline dose mg/m^2	Mean	Standard deviation	P value
EF	<300	61.64	4.884	0.870 NS
	300 - 400	61.83	4.130	
	>400	63.00	1.414	
FS	<300	38.00	3.098	0.533 NS
	300 - 400	39.25	2.800	
	>400	38.00	0.000	

MPI	<300	0.3845	0.02659	0.125 NS
	300 - 400	0.3608	0.02906	
	>400	0.3900	0.00000	

NS: not significant

Discussion

Anthracyclines are commonly used drugs in the therapy of childhood malignancies. They have been well known to cause cardiotoxicity years after completion of chemotherapy, which has been documented extensively in western literature. In our study 25 patients of childhood cancer survivors, who received anthracyclines and evaluated for anthracycline induced cardiotoxicity during the therapy, were evaluated for late anthracycline induced cardiac dysfunction with various electrocardiographic and echocardiographic parameters.

Mean age at diagnosis of malignancy was 7 years 4 months and mean duration after completion of anthracycline therapy was 5 years 6 months. 60% of cases were male and 40% were female. In our study, most of the cases were in 300-400 mg/m^2. 11 cases (44%) were in <300 mg/m^2, 12 cases (48%) were in 300-400 mg/m^2 and 2 cases (8%) were in >400 mg/m^2. Mean age of <300 mg/m^{2}group was 16 years 5 months, 300-400mg/m^2 group was 13 years 7 months, and >400 mg/m^2 group was 12 years. Among 25 cases ALL was 76%, lymphoma was 20%, and hepatoblastoma was 4%. In our study, heart rate was abnormal in 3 cases (12% - one with sinus tachycardia and two with sinus bradycardia) which were statistically not significant. Heart rate abnormalities were most commonly seen in acute anthracycline toxicity. In a study done by Barry, there was statistically significant tachycardia in childhood cancer survivors [5]. Steinhertz and associates who studied the clinical course of late symptomatic anthracycline cardiomyopathy found conduction abnormalities in 14/15 patientsm [6].

In our study, there was significant increase in QTc interval, decrease in QRS amplitud which were consistent with previous studies done by Simbre [7]. In Horacek *et al* study, there was statistically significant increase in QTc interval and decrease in QRS voltage [8]. Decreased total QRS voltage in the limb leads and prolonged QTc interval on ECG correlated with systolic and diastolic LV dysfunction on ECHO [8].

Fractional shortening was significantly improved as compared to earlier study [7]. In a study done by Lipshulzt *et al*, the mean fractional shortening was significantly depressed after therapy, improved, and then became significantly more depressed [9]. The change after the completion of therapy was statistically significant (p=0.001). The low-dose group had relatively normal fractional shortening; the mean in the high-dose group was nearly 3 SDs below normal at the last follow-up. Left ventricular fractional shortening differed significantly between the low and high-dose groups (p=0.001) and between the moderate- and high-dose groups (p=0.001). In earlier study by Simbre also there was a significant decrease in fractional shortening during anthracycline therapy, which was improved significantly after 5 years 6 months of follow-up [7]. All other electrocardiographic parameters and echocardiographic parameters were normal. There was no statistically significant difference of electrocardiographic and echocardiographic parameters between the 3 cumulative anthracycline dose groups.

Conclusions

There was no evidence of electrocardiographic and echocardiographic evidence of delayed cardiac dysfunction in our subjects, who had received anthracyclines for therapy of

various childhood malignancies. MPI was a sensitive noninvasive technique for detection of cardiac dysfunction as it is independent of arterial pressure, heart rate, ventricular geometry, atrioventricular valve regurgitation, afterload, and preload in patients who are in a supine position. We plan to follow up all these subjects with ECG and Echocardiogram for monitoring the cardiac function as per the guidelines. Long term follows up with cardiac functional assessment is required for early detection of delayed cardio toxicity due to anthracyclines.

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