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Anthracycline Induced Cardiac Complications in Childhood Hemato-Oncological Malignancies in a Tertiary Care Hospital

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Abstract
Background*: Anthracycline induced cardiac complications are one of the most common causes of morbidity and mortality in childhood hemato-oncological malignancies despite recent advances in the diagnosis and treatment. Anthracycline causes cardio toxic effects during treatment when the level exceeds the cumulative dose.* ***Aims and Objectives:*** *This was aimed to evaluate the cardiac complications with anthracycline and to determine associated electrocardiogram (ECG) and echocardiogram (ECHO) change with anthracycline in hemato-oncological malignancies.* ***Materials and Methods****: The present study was conducted from January 2018 to December 2018 on sixty-nine diagnosed children with hemato-oncological malignancies between five to fifteen years irrespective of sex. A detailed history along with a complete blood count, biochemical investigations, chest x-ray, bone marrow aspiration, immunophenotype and other relevant investigations were performed. ECG, ECHO was done in all patients at initial presentation and during reassessment. The children were treated with protocol UKALL-XII, Hyper-CVAD, R-CHOP, ATRA+doxorubicin, Doxorubicin+Cytarabine, and ABVD. Blood level of anthracycline was done during reassessment of the patients.* ***Results:*** *Among the hematological malignancies, boys were 46 and girl 23. Acute lymphoblastic leukemia (ALL) was the most common 39.1% followed by acute myeloid leukemia (AML) 18.8% and Hodgkin's disease (HD) 17.3%. The mean cumulative dose of doxorubicin was 265.2±89.3 mg/m^2 and daunorubicin270.6±59.6mg/m^2 among all malignancies. None of the patient found QRS duration more than 120 seconds. One child had QT interval more than 450 ms (p=0.001). The ECHO showed significant difference in ejection fraction (EF) during reassessment. Left ventricular dysfunction (less<50%) were found in 17% children and significant reduction in EF (p=0.001) with significant reduction in diastolic dysfunction (p=0.001).Ten (14%) children treated with R-CHOP, two (2.8%) Hyper-CVAD, twenty-five (36.2%) UKALL-XII, twelve (17.39%) ABVD, thirteen (18.8%) Doxorubicin+Cytarabine 3+7, and seven (10%) ATRA+ADM protocol. Most of the hematological malignancies treated with R-CHOP found left ventricular dysfunction. The left ventricular dysfunction in Hodgkin's disease was statistically significant (p=0.003).Four (66%) children had developed left ventricular dysfunction. Eight patients treated with doxorubicin developed left ventricular systolic dysfunction, only one with daunorubicin.* ***Conclusions:*** *The ECG, QRS voltage change, prolong QTc interval, and left ventricular systolic dysfunction are common with anthracycline treated hemato-oncological malignancies with a cumulative dose>250 mg/m^2.Decrease QRS voltage more than 35% from base line was associated with left ventricular dysfunctionin Hodgkin's disease.*

Keywords*: Anthracycline; Electrocardiography; Echocardiography; Ejection fraction; Cumulative dose; Hematological malignancies.*

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I. Introduction

The effect of anthracycline based chemotherapy on human heart may be manifested differently in different individuals. The most typical clinical manifestations of cardiac muscle damage are as follows: asymptomatic ECG abnormalities, mild blood hypotension, cardiac arrhythmias, electrical conduction dysfunction, myocarditis, pericarditis, acute myocardial infarction, heart failure, and chronic dilated and or restricted cardimyopathy[1-5].

Modern cancer therapies have brought a major breakthrough in pediatric oncology within the last 30 years. Owing to this, it is able to cure approximately 70-80 % children and adolescents with cancer, and in some types of cancer the survival rates are as high as 100 % provided that the diagnosis has been made early enough[6,7]. The efficacy of cancer treatment depends on the degree of damage to the malignant cell population. That is why a single chemotherapy regimen may include several agents, each of them having a different mechanism of action on tumor cells. As a result, they show a cumulative adverse effect on various organs and organ systems in the body.

Anthracycline are antibiotic, anti-neoplastic agents that were discovered in 1963, when a red fluorescent dye was isolated from fermentation of broth of the bacteria *Streptomyces peucetius*. Anthracycline induced cardio toxicity is termed type I chemotherapy induced cardio toxicity which is characterized by the presence of free-radical formation[8]. These radicals may be responsible for lipid per oxidation and DNA breaks[9].The toxic effect of anthracyclines on cardiovascular system leads to the direct loss of cardiomyocytes, decreases cardiac muscle contractility and damage to the micro-vasculature. Furthermore, by affecting cardiac progenitor cells and fibroblasts, anthracyclines make it more difficult for the already-weakened heart to recover from injuries and activity of other stressors, such as co morbidities or individual sensitivity[10].

Being an important side effect of anthracyclines, cardio toxicity may limit the efficacy of cancer therapies in the acute phase (during treatment) and induces long term sequelae which are observed years after treatment completion in childhood cancer survivors. Cardiovascular complications differ in type and severity depending on the actual cancer treatment. Cancer survivors tend to develop heart failure, ischemic heart disease and cerebro-vascular incidents more often than the general population. The cardiovascular mortality rates among childhood cancer survivors are less than tenfold higher compared to the age-matched controls[11,12]. Chemotherapy, radiation therapy and new biological therapies, used as a standalone treatment or in combination constitute an important risk factor and predispose the patients to develop such complications.

Anthracyclines induced cardiac effects were initially categorized into two distinct forms: early and late toxicity[13]. Early cardiac manifestations of anthracycline administration probably represent the actual insult, which later progresses to overt cardiomyopathy. These manifestations may be sufficiently subtle as not to be considered a serious medical concern. The importance of the initial injury is usually underappreciated as it almost never requires treatment[13].Anthracycline treatment is associated with changes in electrical activity of the myocardium. Prolonged QTc interval represents a risk for development of malignant ventricular arrhythmias. Decreased QRS voltage and prolonged QTc interval after anthracycline treatment could be correlated with LV dysfunction on ECHO[14].The most common findings seen are electrocardiographic changes are usually in the form of repolarization changes involving the ST-segment and the T-wave, and dysarythmia usually in the form of supra-ventricular or ventricular ectopic, which are seen often and are only rarely sustained or malignant[15].

Mechanisms of anthracycline induced cardio toxicity include the generation of excess reactive oxygen species and formation of iron complexes. Recently, it was revealed that anthracyclines can inhibit topo-isomerase 2β causing double-stranded breaks in DNA, which can lead to cardiomyopathy and death[16]. Risk factors for anthracycline-induced cardio toxicity include the lifetime cumulative dose, infusion regimen, pre-existing cardiac disease, and cardiovascular risk factors, such as hypertension, diabetes, dyslipidemia, obesity, and older age (>65 years)[17]. The increase in the incidence of cancers in breast, colon-rectum and in non-Hodgkin's lymphoma, age increases indicates the aging process as a risk marker for greater development of cardio toxicity in the population[18].Anthracyclinecauses cardiac toxicity which was significantly associated with age. A study included 4,018 patients with a median age of 49, where incidence of anthracycline induced cardio toxicity increased steadily with age ($p=0.0002$)[19]. Early toxicity is more common in the elderly and is probably related to underlying and unrelated heart disease that exists in the aging population and associated likelihood of increased oxidative stress. Early toxicity is common with large single dose of doxorubicin[20]. Late toxicity is related to the cumulative dose of doxorubicin with the injury resulting from the death of myocytes. The more recent data suggested that doxorubicin is substantially more cardio toxic than was originally believed[21].

The total cumulative dose of anthracyclines is the most significant risk factor for cardiac dysfunction.[22]There is a clear relationship between the occurrence of anthracycline cardio toxicity and the cumulative dose of the drug. In a retrospective analysis, it was found that when a patient receives a cumulative dose of doxorubicin at 400, 550 and 700 mg/m^2, the incidence of cardio toxicity is 3, 7 and 18%, respectively, with dose-limiting toxicity. Therefore, it was recommended that the cumulative dose of doxorubicin should not exceed 550 mg/m^2. The children treated with epirubicin, cumulative dose recommendation should not exceed

(900 mg/m^2)[19]. A risk analysis study of 1,097 patients with metastatic breast cancer done who had previously been treated with epirubicin; maximum cumulative dose for epirubicin treatment was determined according to patient's risk level, to keep the incidence of congestive heart failure below 5%. The results showed that for patients at an average age of 40, without other risk factors for congestive heart failure the recommended cumulative dose was 806 mg/m^2, and average age of 70, and maximum cumulative dose was (609 mg/m^2)[23].

It was observed that the estimated cumulative percentage of congestive heart failure was 5% at dose 400mg/m^2, 26% at dose of 550mg/m^{2}and 48% at dose (700mg/m^2)[21].There is no sensitive or specific test that reliably predicts which patient might develop cardiac dysfunction after treatment with anthracycline[24]. The non-invasive tests have sub-optimal predictive value that is the manifestation of false-positive and false-negative results. At low cumulative dosages, when likelihood of a decreased ejection fraction (EF) due to anthracycline is small, false-positive results may exceed the incidence of true-positive results.

Non-invasive test can result in the recognition or confirmation of early or sub-clinical abnormalities in selected patients. Two-dimensional (2D) echocardiography is the most widely available method for monitoring left ventricular ejection fraction. Advantages include portability and capability of assessing other measures of myocardial dysfunction as well as other cardiac lesions (valve disease). Measurement of resting global left ventricular (LV) function using either first pass or equilibrium multi-gated blood pool imaging scan is an established technique for monitoring anthracycline cardio toxicity. However, it is used less often than echocardiography. Conduction abnormalities are also a nonspecific finding; they are the manifestation of congestive heart failure but may be related to other factors as well; not helpful as a predictive parameter for follow-up patients received doxorubicin[25].

All patients should undergo a baseline measurement of EF using echocardiography or a nuclear technique. The baseline results are useful for later comparisons and identify patients with cardiac risk factors and thus require close monitoring. The patients with normal systolic function and no risk factors usually tolerate 550 mg/m^2 doxorubicin or the maximum recommended cumulative dose of other anthracyclines. Toxicity at cumulative doses below two-third of maximal recommended dosage (300 mg/m^2 doxorubicin) is unusual. The cumulative dose range from two-third to the maximally recommended dose (300-550 mg/m^2 doxorubicin), patients should be evaluated by a clinical history and follow-up echocardiogram should be performed either at that time or 3 months aftertherapy[25].

II. Aims And Objectives

Aims:

- To determine anthracycline induced cardiac complications in hemato-oncological malignancies in a tertiary care hospital.

Objectives

a) General objective:

- To evaluate cardiac complications with anthracycline.

b) Specific objective:

- To determine associated ECG, ECHO changes with anthracycline.
- To determine the presence of association with demographic and clinical variables with anthracycline.

III. Materials And Methods

Study Place: Department of Pediatric Hematology and Oncology.
Study Design: Prospective observational study.
Study Location: Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
Study Duration: January 2018 to December 2018.
Sample Size: Sixty-nine diagnosed children of hemato-oncological malignancies.
Sample Size Calculation: The sample size was estimated on the basis of single proportion design. The target population from which 127 sample were randomly selected from the record sheet. Thirty-nine children failed to fulfill the inclusion and exclusion criteria. From the remaining patients, nineteen had withdrawn their enrollment. Finally, sixty-nine children were selected for final calculation in the study with 21% drop out. We assumed the confidence interval 10% and confidence level 95%.
Subjects and Selection Methods: The study populations were extracted from hemato-oncological malignancies who presented at Pediatric Hematology and Oncology Department of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh that underwent relevant investigations for diagnosis.
Inclusion Criteria:

1. Five to fifteen years.
2. Both sexes.
3. Written consent to enroll in the study.

4. Diagnosed case of hemato-oncological malignancies: acute lymphoblastic leukemia (ALL-27), acute myeloid leukemia (AML-13), acute promyelocytic leukemia (APML-7), Hodgkin's disease (HD-12), and non-Hodgkin's lymphoma (NHL-10).
5. The children who received protocol based chemotherapy (UKALL-XII)[26], (Hyper-CVAD)[27],(DA 3+7)[28],(ABVD)[29], (R-CHOP)[30].
6. The children with ejection fraction more than 50%.

Exclusion Criteria:

1. Hemato-oncological malignancies below five years and above fifteen years.
2. Hemato-oncological malignancies other than included malignancies.
3. Received any chemotherapy before enrollment in the study.
4. The children who received drugs which can prolong QT interval.

IV. Methodology

The parents were properly counseled about the aims of the study and written consent was taken from the parents. A well-designed questionnaire was used to collect the data of the enrolled patients. The questionnaire included socio-demographic characteristics such as age, sex, height, weight, drug which prolong QT interval, received any chemotherapy before recruitment ECG, ECHO. To observe cardiac complications, electrocardiogram (ECG) and echocardiogram (ECHO) were done initially and during reassessment of patients with anthracycline therapy, and to find out the association in the ECG and ECHO with anthracycline. Investigations like; complete blood count, biochemical investigations, chest x-ray, bone marrow aspiration and immunophenotype and other related investigations were performed in favor of diagnosis. Interpretation of ECG and ECHO were performed in every patient. The blood level of anthracycline was done during chemotherapy to ensure the cumulative dose.

The ALL children had received protocol UKALL-XII[26]and some had high initial white count and others had bad prognostic factors who received protocol Hyper-CVAD[27] with cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high dose methotrexate and high dose cytarabine. The AML children were treated with the protocol DA 3+7[28] with doxorubicin for three days and cytarabine for seven days. The AML-M_3 (acute promyelocytic leukemia) were treated with protocol ATRA+ doxorubicin (ADM)[28], ATRA plus four dose doxorubicin on each other day. The HD children were treated with protocol ABVD[29] with adriamycin, bleomycin, vinblastine, and decarbazine. The NHL was treated with protocol R-CHOP[30] with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

In general, leukemic children were reassessed after completion of induction therapy and interim reassessment was also performed in lymphomas children. Cardiac complains were also evaluated time to time during therapy. The ECG was done in every patients and the record was interpreted. Corrected QT (QTc) was obtained directly from the device. ST-T changes were identified when ST depression or T-wave changes were noted. QRS voltage was calculated as the voltage of net number of small squares in the vertical length of lead II (R wave-S wave). The QRS duration was measured directly by the device.[31]

Statistical analysis

Collected raw data were organized into a statistical format and analyses were performed using statistical package for social science (SPSS), a software version 21.0. All continuous and demographic data were expressed as mean±SD and categorical data in percentage (%). Chi-square test was done for qualitative variables; paired t, unpaired t-test and ANOVA were done for quantitative variables. The p-value of less than 0.05 and confidence interval 95% was taken as the minimum level of significance.

V. Results

Sixty-nine children of various hematological malignancies were included in the study. The boys were 46(66.66%) and girl 23 (33.33%). The boy's and girl's ratio was 2:1. The individual number and age distribution of hematological malignancies showed separately. The most common disease in terms of frequency was ALL 39.1% followed by acute myeloid leukemia (18.8%) and Hodgkin's disease (17.3%)(Table 1).

Table 1: Hematological malignancies based on number and age (n, 69).

Hematological malignancies	Number of patients (%)	Mean±SD (Age)
Acute lymphoblastic leukemia	27(39.1)	7.45±2.35
Acute myeloid leukemia	13(18.8)	9.25±1.50
Acute promyelocytic leukemia	07(10.1)	8.75±2.75
Hodgkin's disease	12(17.3)	6.50±1.35
non-Hodgkin's lymphoma	10(14.4)	5.45±1.55

Boys were found to be affected more in all the malignancies. Among the boys 71.43% of children were AML-M3. The next common is NHL (70%), AML (69.23%), and ALL (66.67%). In girls, comparatively higher percentage is found in HD (41.67%) followed by ALL (33.33%). Other three malignancies in the girls were found more or less same (Figure 1).

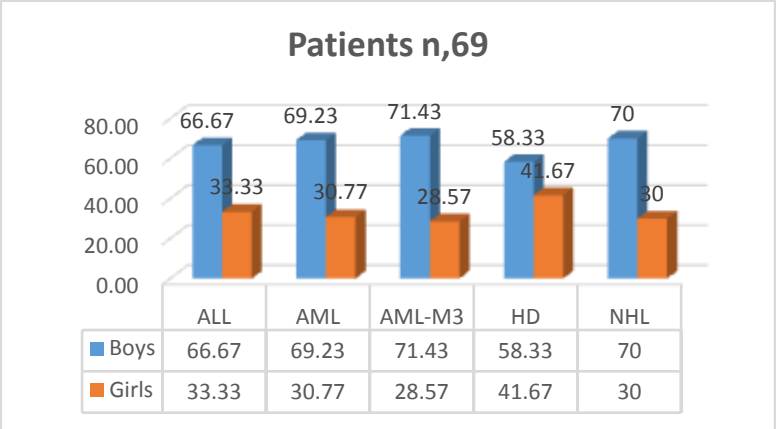

Figure 1: Distribution of hematological malignancies based on sex.

The presentation of hematological malignancies and their diagnosis were documented (Table 2).Fever (100%) and organomegaly was the common presentation in all hematological malignancies. There was anemia in leukemic children. ALL and AML are presented with bone pain. In AML gum hypertrophy and proptosis are found. The special variants of AML (AML-M3) are found with features of DIC. The HD is presented with superior vana caval syndrome and mediastinal mass. Lymphadenopathy, pleural effusion, and ascities were the presentation of NHL.

Table 2: Clinicalpresentationand diagnosis of hematological malignancies patients (n,69).

Hematological malignancies	Presentation	Laboratory investigations
Acute lymphoblastic leukemia	Progressive pallor, fever, bone pain, history of blood transfusion, lymphadenopathy, hepatomegaly	Complete blood count, peripheral blood film,biochemical investigation (serum LDH), chest x-ray, bone marrow aspiration, immunophenotype
Acute myeloid leukemia	Progressive pallor, fever, bone pain, history of blood transfusion, lymphadenopathy, hepatomegaly, gum hypertrophy, proptosis	Complete blood count, peripheral blood film, biochemical investigation(serum LDH), chest x-ray, bone marrow aspiration, immunophenotype
Acute promyelocytic leukemia	Progressive pallor, fever,bone pain, lymphadenopathy, hepatomegaly, gum hypertrophy, history of blood transfusion, proptosis, features of DIC	Complete blood count, peripheral blood film, biochemical investigation (serum LDH), chest x-ray, bone marrow aspiration, immunophenotype
Hodgkin's disease	Mildly pale, generalized lymphadenopathy, features of superior vena caval syndrome, mediastinal mass, hepatomegaly, B-symptoms	Complete blood count, peripheral blood film, biochemical investigation (serum LDH), chest x-ray, bone marrow aspiration, CT scan of chest and abdomen, lymph node biopsy
non-Hodgkin's lymphoma	Mildly pale, lymphadenopathy, plural effusion, ascities, hepatomegaly,	Complete blood count, peripheral blood film, biochemical investigation (serum LDH), chest x-ray, bone marrow aspiration, CT scan of chest and abdomen, lymph node biopsy

Ten children (14%) children were treated with R-CHOP protocol, two (2.8%) children with Hyper-CVAD protocol, twenty-five (36.2%) treated with UKALL-XII protocol, twelve (17.39%) with ABVD protocol, thirteen with (18.8%) with Doxorubicin+Cytarabine 3+7 protocol, and seven (10%) with ATRA+ADM protocol.

The cumulative dose of anthracycline varied from one malignancy to other. Maximum cumulative dose of doxorubicin in HD was 480 mg/m^2, daunorubicin was 490 mg/m^2. Mean cumulative dose with doxorubicin was 215.2±89.3 mg/m^2 and daunorubicin was 260.6±59.6 mg/m^2 (Table 3).

Table 3: Cumulative dose of anthracycline during treatment in hematological malignancies (n, 69).

Anthracycline	Malignancies	Minimum (mg/m^2)	Maximum (mg/m^2)	Mean±SD (mg/m^2)
Doxorubicin	ALL	115	350	265.2±89.3
	AML	120	400	
	AML M3	130	450	
	HD	150	480	
	NHL	140	470	
Daunorubicin	ALL	135	450	270.6±59.6
	AML	140	470	
	AML M3	170	450	
	HD	190	490	
	NHL	210	485	

The ECG change was recorded in all patients. There was no patient found with QRS duration more than 120 seconds. One of the child had QT interval more than 450ms which was statistically significant (p=0.001). The ECHO showed statistically significant difference during reassessment with ejection fraction, left ventricular dysfunction (less than 50%) in 17% and diastolic function (p=0.001)(Table 4).

Table 4: Electrocardiograph and echocardiograph changes in baseline and during reassessment (n,69).

Parameters		Baseline mean±SD	Reassessment mean±SD	p value
ECG	QRS voltage(mV)	0.587±0.077	0.529±0.077	0.001
	QRS duration(ms)	93.56±5.05	91.45±0.077	0.013
	QT interval (ms)	378.7±11.8	498.32±13.8	0.001
	ST-T changes (%)	3	4	0.004
ECHO	Mean ejection fraction	68.76	61..05	0.001
	Left ventricular dysfunction (EF<50%)	Absent	12(17.39)	0.001
	Diastolic dysfunction (%)	15(21.73)	21(30.43)	0.001

Left ventricular dysfunction with the diagnosis among the hematological malignancies was Hodgkin's disease which was statistically significant (p=0.003). Most of the hematological malignancies treated with the protocol R-CHOP had found left ventricular dysfunction. Here, four (66%) children had left ventricular dysfunction. Eight children treated with doxorubicin had developed left ventricular systolic dysfunction and only one children treated with daunorubicin (Table 5).

Table 5: Left ventricular systolic dysfunction at diagnosis, with treatment protocol and treated with anthracycline (n,69).

Diagnosis	Left ventricular systolic dysfunction		p value
	Present	Absent	
Acute lymphoblastic leukemia (n,27)	2 (7.40)	25 (92.59)	0.75
Acute myeloid leukemia (n,13)	1 (7.69)	12 (92.30)	0.64
Acute promyelocytic leukemia (n,7)	0 (0)	7 (100)	0,84
*Hodgkin's disease (n,12)	2 (16.66)	10 (83.33)	0.003
non-Hodgkin's lymphoma (n,10)	3 (30)	7 (70)	0.72
Treatmentprotocol	Left ventricular systolic dysfunction		
	Present	Absent	Total
R-CHOP	04	06	10
Hyper-CVAD	02	0	02
UKALL-XII	0	25	25
ABVD	0	12	12
Doxorubicin+Cytarabine 3+7	0	13	13
ATRA+ADM	0	07	07
Total	06	63	69
Treatment with Anthracycline	Left ventricular systolic dysfunction		
	Present	Absent	Total
Doxorubicin	8	37	45
Daunorubicin	1	23	24
Total	09	60	69

*Significant

VI. Discussion

We found no significance difference in age and sex in hematological malignancies. Male preponderance was observed in anthracycline related cardiac complications.

Although doxorubicin has become one of the most effective chemotherapeutic agents, it was noted early on that its use was complicated by the development of heart failure[19,32]. In a retrospective analysis of over 4000 patients receiving doxorubicin, 2.2% of the patients developed clinical signs and symptoms of congestive heart failure[19].We do not have any document of cardiac complications with hemato-oncological malignancies in children receiving anthracycline. We stratified hemato-oncological malignancies e.g., ALL, AML, HD, NHL. Our study protocol was more or less consistent with the previous study,[33] but it was not consistent with other observations[14].

The cardio toxicity caused by anthracylcine may occur early or late during a course of treatment, or it may appear months or even years after treatment. Early toxicity is unusual, and when it occurs, it usually presents as a myopericarditis, which may progress to significant cardiac dysfunction within a few weeks of the first administration of the drug[15]. We did not find any single patient with sign and symptoms of cardiac toxicities before chemotherapy which was consistent with the findings of other authors[33]. Early toxicity is more likely to occur in elderly patients or in patients who have received large single doses and it is more common in patients treated with daunorubicin than with doxorubicin.

We applied different protocol of treatment specified for our hemato-oncological malignancies according to guidelines[26-30]. So, the dose of anthracycline and the cumulative dosages differ from one malignancy to other. The mean cumulative dose of anthracycline in our study: Doxorubicin265.2±89.3 mg/m^2 and Daunorubicin270.6±59.6 mg/m^2 which was consistent with the observations of previous authors[14].The higher incidence of cardiac toxicity observed when two drugs are administered within a short time which may interfere with the pharmacokinetics of doxorubicin, leading to higher systemic levels of both drugs[34-36]. The combination of two or more drugs having cardio toxic effects should be avoided not to exceed the cumulative dose. Alternatively, the apparent increase in toxicity may simply reflect the easier diagnosis of heart failure in patients undergoing sequential monitoring of cardiac function.

In our study a significant number of child 54 (78%) had developed infections in the form of neutropenia 37(68.5%), mucoscitis 13(24%), and diarrhea 4(7%) during the course of treatment. These children were successfully managed with supportive therapy. Only 15 (21%) had completed the protocol based chemotherapy without any event.

One child with AML-M3 had developed ATRA-syndrome three days of beginning of chemotherapy having the signs and symptoms of coagulopathy. As the child had received intensive chemotherapy regimens associated with severe toxicity derived from prolonged cytopenia which in turn results in life-threatening hemorrhages and or infections and managed with blood and blood products along with supportive care. Ameliorating the disease associated coagulopathy as well as long-term outcome, use of ATRA has been associated in a fraction of cases with a newly described severe complication as ATRA-syndrome[37], incidence and morbidity seems to be reduced when chemotherapy is administered concomitantly[38].Their findings are consistent with our observations. In this study, none of the patients treated with R-CHOP developed any signs and symptoms of cardiac complications which were not consistent with the previous authors[39], where 10% of patients developed clinical features of congestive heart failure.

We did not find any children having QRS duration more than 120ms instead there was 0.587±0.077mV (baseline and 0.529±0.077mV (reassessment) though there were no electrolyte abnormalities during routine investigations. The QT interval also has been significantly increased from baseline (378.7±11.8) to reassessment (498.32±13.8).A decrease in QRS or prolongation of QTc interval increases the risk of developing cardiomyopathy in pediatric patients receiving anthracycline therapy. Higher total anthracycline doses are associated with decreases in the QRS and prolongation of the QTc interval. The decrease in QRS after therapy was greater in patients who developed cardiomyopathy[40]. Another study found no significant difference in QRS duration among the patients with NHL treated by CHOP[41]. Some authors reported a significant prolongation in QTc from 414.7±16.0 to 430±18.4, they reported five patients (19.2%) developed QTc>450ms[14]. ECGs are a potential noninvasive, inexpensive tool for prediction of anthracycline induced cardiomyopathy.

We found the children with statistically significant difference who received anthracycline had developed left ventricular dysfunction 12(17.39%) and diastolic dysfunction 21(30.43%) during reassessment compared to baseline (Table 4).Some authors reported subclinical LV dysfunction by global longitudinal strain (GLS) 22%. There was an increase in prevalence of LV diastolic dysfunction in the subgroup more than 11% reduction in GLS. No clinical risk factors were predictive of subclinical LV dysfunction, thus emphasizing the need for all patients to be monitored for deterioration in both systolic and diastolic function following anthracycline treatment[42].

Most of the hemoto-oncological malignancies who developed left ventricular dysfunction was Hodgkin's disease (p=0.003) (Table 5). Our observations were consistent with other authors[43], where they investigated echocardiography changes of left ventricular function in 79 patients with non-Hodgkin lymphoma or Hodgkin's disease who were treated by chemotherapy containing doxorubicin. In 22% patients diagnosed

during treatment showed significant gradual decline of left ventricular ejection fraction (change>10% or a drop of EF below 50%) after a cumulative dose of 185+/-52 mg/m^2 doxorubicin (median 200 mg/m^2). Our observations are disappointed by other authors[41], where a significant reduction in EF in patients found with NHL treated by anthracycline.

We observed 4 children with protocol R-CHOP and 2 with Hyper-CVAD who developed left ventricular systolic dysfunction. They were managed meticulously without any significant event. Our findings were consistent with other authors[44], where Hyper-CVAD was associated with significantly better complete response rates, complete response in duration, survival and the long-term follow-up results of Hyper-CVAD were favorable. The patients with NHL lymphoma were treated by R-CHOP protocol associated with a significant reduction in EF[45].There were significant events of cardiovascular complications in patients treated by CHOP[39].Some authors found no significant difference in toxicity caused by R-CHOP as compared to CHOP[46]. We have found only a case who developed left ventricular systolic dysfunction with daunorubicin, may be due to less cardio toxic effect in comparison to doxorubicin (Table 5).

In our study, eight children with doxorubicin and one with daunorubicin developed left ventricular systolic dysfunction but the cumulative dose are different from one another. The mean cumulative dose of doxorubicin induced left ventricular systolic dysfunction was 265.2±89.3 mg/m^2 and daunorubicin 270.6±59.6 mg/m^2(Table 3). Having low cumulative dose of doxorubicin, a significant number of patient had found systolic dysfunction than patients of high cumulative dose of daunorubicin. Cumulative dose causing LV dysfunction in our observations was 265.2±89.3 mg/m^2, which was not consistent with other authors:(150mg/m^2)[47], (200mg/m^2)[41]. Most clinicians limit the cumulative dose of doxorubicin 400-450mg/m^2, but considerable cardiac damage is now known to occur at cumulative dosages considerably below this level[48], which was consistent with our findings. We observed a significance decrease in QRS voltage more than 35% from base line to develop left ventricular dysfunction (p=0.001) which was consistent with other previous observations[14,49,50].

VII. Conclusions And Recommendations

Decrease QRS voltage in the limb leads and prolong QTc interval on the ECG has significant correlation with systolic and diastolic LV dysfunction on the ECHO with anthracycline (doxorubicin). There is significant association in ejection fraction, left ventricular systolic and diastolic dysfunction with anthracycline. Left ventricular dysfunction is more common with Hodgkin's disease treated with R-CHOP protocol. Decrease QRS voltage more than 35% from base line is associated with left ventricular dysfunction. Further studies on a larger number of patients will be needed to prove whether these ECG and ECHO changes could serve as an accessible and non-invasive screening method indicating LV dysfunction after anthracycline treatment. Further results are eagerly awaited from ongoing control trials of cardiac safety with long-term anthracycline therapy, either alone or in combination with other cardio toxic agents.

Limitation of the study

This is a small size single center study.

Follow-up

The children were on regularly follow-up at the outpatient department for last two years. Their hematological and biochemical profile were performed weekly. The ECG was done every six months' interval, and ECHO every twelve-month interval to aware about the late cardiac complications of anthracycline. During follow-up there was no major complication other than infections and neutropenia which was managed successfully.

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Self-funding

Ethical Issue

The confidentiality and responsibility of patients have followed the method of the World Medical Association Declaration of Helsinki, 2000.

Conflict of interests

The author declares no conflict of interests.

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