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Cardiotoxicity in Children With Acute Ieukemia Treated by Anthracycline; Detected by Cardiac Troponins and Echcocardiography

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Abstract

Background and objectives: the use of anthracycline antineoplastic agents has conducted to improved pediatric malignancies' outcomes, yet their use is limited by their potential cardiotoxic effects. Thus, children who have received anthracyclines require cardiac evaluation periodically. The serum levels of cardiac troponins have been shown to be elevated in response to severity of cardiac dysfunction. The aim of our study was to investigate the role of serum levels of cardiac troponin and echocardiography as sensitive markers for anthracycline-induced cardiotoxicity in children with malignancy. **Methods:** we carried out this study at Nanakali Hospital, Pediatric Hematology and Oncology unit. We measured plasma high sensitive cardiac troponin T in 24 patients who received anthracyclines for their malignancy at cumulative doses of 75-310mg/m2, between Feb 2017 and Feb 2018. Evaluation of the patients for cardiac functions included physical examination, chest X-ray and echocardiography in addition to cardiac troponins. **Results:** Of the 24 patients, 3 (12.5%) had abnormal cardiac functions by echocardiography. Serum troponin level in two of them was significantly elevated. Physical findings of the patients were significant. Chest X-ray in 2 (8.3%) showed radiological findings. **Conclusions:** Serum troponin concentration and Echocardiography may be practical and sensitive indicator of abnormal cardiac function in children receiving anthracycline therapy.

Keywords: Cardiotoxicity; Acute Leukemia; Cardiac Troponins.

Introduction

The introduction of anthracycline (ANT) antineoplastic antibiotics to the chemotherapy of malignant neoplasms has been one of the major successes of cancer medicine. This is particularly evident in pediatric oncology, where the 5-year survival rate for childhood cancer has increased from 30% in the 1960s to 70–80% today[1]. The relatively high survival rate of these individuals, however, is tempered by the high incidence of treatment-related health complications throughout their lifespan. Such complications include clinical or subclinical cardiovascular damage, lipid abnormalities and an increased incidence of obesity1, risks that may persist up to 45 years after treatment[2]. Cardiotoxicity can arise acutely, during or shortly after treatment and regardless of dose in the form of cardiac arrhythmias, for example, sinus tachycardia, ventricular, and supraventricular tachycardia. Pericarditis, potentially fatal congestive heart failure, and acute pulmonary edema can also occur during doxorubicin therapy caused by myocyte necrosis as a result of increased cardiac apoptosis and alteration of cardiac cytochrome P450 expression and arachidonic acid metabolism[3, 4].

The American Heart Association's class I recommendation for chil¬dren receiving anthracycline treatment is serial monitoring by echocardiography starting at diagnosis and throughout treatment, using either M mode echocardiography, Doppler M analysis, 2D transthoracic echocardiography or, if possible, transesophageal echocardiography[5]. Similarly, the Children's Oncology Group recommends the use of serial echocar¬diography to monitor cardiac status in this population

The serum level of cardiac troponin T is an accurate surrogate for acute myocardial injury in children[7, 9] specifically that related to doxorubicin10 and the maximal cardiac troponin T level during doxorubicin therapy is significantly correlated with the cumulative dose of doxorubicin and with subsequent structural abnormalities of the left ventricle seen on echocardiograms in these

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patients[8]. A continuous 48-hour infusion of doxorubicin was not found to be more cardioprotective than bolus administration in patients with childhood acute lymphoblastic leukemia[11].

Despite more than three decades of use, it is still unclear exactly how anthracyclines exert their chemotherapeutic activity and induce cardiotoxic changes. The antineoplastic activities of doxoru¬bicin seem, at least in part, to be derived from the inhibition of topoisomerase II, free-radical gen¬eration, activation of signaling pathways, DNA intercalation and binding and apoptosis[12, 13].

A major pathogenic pathway links the generation of radical oxygen species (ROS) and lipid peroxidation of the cell membrane to cardiomyocyte injury acquired during anthracycline exposure. Anthracyclines can induce ROS generation both enzymatically and through the formation of anthracycline–iron complexes[14, 15].

The risk of clinical cardiac injury in both children and adults concurs with increases in the anthracycline cumulative dose. It is reported that the estimated incidence of developing clinical heart failure induced by anthracycline, is raised with both time since treatment and cumulative anthracycline dose (5.5% at 20 years after the start of anthracycline therapy if treated with a cumulative dose less than 300 mg/m2, and 9.8% if treated with a cumulative dose exceeding 300 mg/m2 over a mean of 8.5 years[16]. The aim of our study was to investigate the role of serum levels of cardiac troponin and echocardiography as sensitive markers for anthracycline-induced cardiotoxicity in children with malignancy.

Patients and methods

This prospective study was conducted at Nanakali Hematology and Oncology Teaching Hospital/pediatric oncology department in Erbil, Kurdistan region/ Iraq from Feb 2017 to February 2018. Twenty four cases out of forty-eight cases with newly diagnosed Acute Leukemia, whom diagnosis was confirmed by complete blood picture, bone marrow aspiration and biopsy and flowcytometry; all were done at Nanakali Hospital, of which twelve female and twelve male aged 1-15 years were enrolled in this study. All cases with existing cardiac disease or receiving any medication affecting cardiac function and children with any congenital anomaly had been excluded from this study and the rest of the patient didn't agree to participate in the study. A full history has been taken and a thorough clinical examination has been performed. Basic investigations have been sent including renal and liver function tests, serum uric acid level, and fasting blood sugar. Written consent was obtained from all parents. The study had been approved by ethical committee of Kurdistan board for Medical Specialties.

All patients were stabilized hemodynamically then treatment was initiated for all cases according to Iraqi modified protocols for Acute Leukemia, which includes Doxorubicin at induction of remission and delayed intensification each on 25mg/ m2 for Acute Lymphoblatic Leukemia(ALL) for total of 7 doses according to United Kingdom Acute Lymphoblastic Leukemia (UKALL)17 protocol, and 50mg/ m2 of Daunorubicin for Acute myeloid Leukemia(AML)18 for three doses at each induction cycle according to AML 15 version 3.12 protocol. AML- Trial 15 Protocol for AML and UKALL for ALL are shown in the Tables 1, 2.

Table (1): UKALL protocol for induction of ALL[17]

Drugs	Dose	Days	Total doses
Prednisolone	40mg/m^2	From day 1	5 weeks
Vincristine	1.5mg/m^2	Day 8,15,22,29	4 doses
Daunorubicine	25mg/m^2	Day 8,15,22,29	4 doses
L-aspaarginase	10000IU/m^2	Every other day	Total 9 doses
IT-MTX*		Day 8,15	2 doses

* IT; intrathecal, MTX; methotrexate

Table (2): TRIAL -15 protocol for induction of AML[18]

Drugs	Doses	Days	
Doxorubicine	50mg/m^2	1,3,5	
Cytaribine	100mg/m^2	10 days	20 doses
PRD eye drop*	2 hourly	10 days	
IT-MTX,H.C.**, cytaribine		Beginning of induction	One/induction cycle

* PRD; prednisolone ** H.C.; hydrocortisone,

After completing induction, consolidation or delayed intensification for ALL and induction for AML, patients were sent for echocardiography altogether with high sensitive cardiac troponin T (cTnT hs). Before sending for evaluation patients were treated for fever, infection and anemia was corrected. Two echocardiograms were performed for each patient, first one before therapy and second one after receiving treatment. Eight of them were evaluated soon after completing induction, nine of them soon after completing delayed intensification and others at maintenance, in order to assess cardiac status at different times after therapy with anthracyclines.

Echocardiography assessments were all performed using Vivid E9 machine, 3.5 MHz multifrequency transducer by one pediatric cardiologist at surgical specialty hospital/ cardiac center.

For serum cTnT hs, two milliliters of blood were drawn into tubes containing sodium ethylene diamino tetra acetate (EDTA) and aprotinin while the patient was resting in the supine position. Immediately, the blood was centrifuged at 4ºC and plasma was separated. Plasma then was stored at -20ºC until additional processing. Blood samples were all analyzed by one private laboratory.

Chest X-rays were also taken for all patients, and X-ray results were interpreted by an experienced radiologist.

Data were recorded on a specially designed questionnaire, collected and entered in the computer and then analyzed using Statistical Package for Social Sciences (SPSS) version 22 and the results were compared between patients with different variables, with a statistical significance level of < 0.05. The results presented as rates, ratio, frequencies, percentages in tables and figures and analyzed using Chi square.

Results

The study population consisted of 12 boys (50%) and 12 girls (50%). Twenty-two of them were ALL 91% (two of ALL patient were relapsed ALL) and two (8.3%) were AML. Eight patients (33.3%) were evaluated after induction, nine (37%) after delayed intensification, and seven patients (29%) at maintenance therapy. Age of the patients ranged from (1-15 years), with mean (± SD) 4.71(±3.1); no significant association was seen between age of patients and cardiotoxic effect. As of two patients with cardiac abnormalities, one of them was 13 years and the other was 1 year old, Table 3.

Table (3): Difference between normal and abnormal

Variables	Cardiotoxic effects	N	Mean	S.D	P value
Age in years	Normal*	21	4.71	2.47	0.07
	Abnormal**	3	8.17	5.96	

*No cardiotoxicity

There was a significant association between cumulative dose and Serum troponin level, P-value was 0.001. Twenty-Two patients (91.7%) received anthracycline of less than 300 mg/m2 had serum troponin levels less than 14 ng/L, while two patients (8.3%), with Anthracycline dose of ≥300 mg/m2 had troponin level of more than 14 ng/L, Table 4.

Strong association was found between cumulative dose of anthracycline with physical findings (e.g., tachycardia, dyspnoea, cyanosis, hepatomegaly, lung crackles, leg edema...etc), Echocardiography and chest X-ray, (P= 0.001). Majority of Those who received cumulative dose of less than 300 mg/m2 them did not have any significant physical findings, except one patient who had only tachycardia with Echo study having mild reduction in left ventricular ejection fraction(LVEF), though patients who received cumulative dose of ≥ 300 mg/m2 developed abnormal physical findings.

One of the patients with ALL who received >300mg/ m2 had only tachycardia with dyspnoea on exertion, her Echo study showed reduced LVEF. The other patient (AML received 300 mg/m2) developed severe dyspnoea, generalized edema, severe tachycardia with basal lung crackles and hepatomegaly with Echo findings of dilated cardiomyopathy, Table 4.

The only two patients (8.3%) who received higher doses showed abnormal findings on plain CXR. One of them had increased cardiopulmonary ratio, and the other patient

showed huge cardiomegaly with pleural effusion, while the remaining twenty-two 91.7% showed significant findings, (P= 0.001), Table 4.

Table (4): Association between cumulative dose with serum troponin, physical, echocardiography and chest X-ray findings

Cumulative dose	Serum troponin		Tot.l	P-value
	< 14 ng/L	≥ 14 ng/L		
< 300 mg/m^2	22 (100%)	0 (0%)	22(100%)	0.001
≥ 300 mg/m^2	0 (0%)	2 (100%)	2 (100%)	
Total	22 (91.7%)	2 (8.3%)	24 (100%)	
Cumulative dose	**Physical findings**			
	Normal	**Abnormal***	**Total**	
< 300 mg/m^2	21(95.5%)	1(4.5%)		
≥ 300 mg/m^2	0 (0%)	2 (100%)	2 (100%)	0.001
Total	21 (87.5%)	3 (12.5%)	24 (100%)	
Cumulative dose	**Echocardiography findings**			
	Normal	**Abnormal****	**Total**	
< 300 mg/m^2	21 (95.5%)	1 (4.5%)	22 (100%)	0.001
≥ 300 mg/m^2	0 (0%)	2 (100%)	2 (100%)	
Total	21 (87.5%)	3 (12.5%)	24 (100%)	
Cumulative dose	**Chest X-ray findings**			
	Normal	**Abnormal*****	**Total**	
< 300 mg/m^2	22 (100%)	0 (0%)	22 (100%)	0.001
≥ 300 mg/m^2	0 (0%)	2 (100%)	2 (100%)	
Total	**22 (91.7%)**	**2 (8.3%)**	**24 (100%)**	

*Tachycardia, dyspnoea, cyanosis, hepatomegaly, leg edema, lung crackles, murmur etc...

**Dilated cardiomyopathy, Reduced LVEF etc…

***Increased cardiopulmonary ratio, cardiomegaly, pleural effusion etc…

Discussion

The pediatric population is more susceptible to anthracycline induced cardiotoxicity, and there is likely no safe dose in children[19]. The incidence of cardiotoxicity after receiving Anthracycline therapy in childhood is similarly dose-dependent20 and 100% suffered from cardiac abnormalities after being treated with <400mg/m2 of Anthracycline based chemotherapy[21].

In this study among 24 enrolled patients 22 of them received lower cumulative dose less than 300 mg/m2. Only one patient 4.5% of them found to have mild subclinical echocardiography changes, as in a study performed by G. Watts et al, 2.5% of patients were found to have mild abnormal echocardiography, at cumulative dose of <300mg/m2[22]. In this study, only the children who received 300 mg/m2 developed a 100% risk of cardiotoxicity detected by echocardiography, but in study performed by Klaus Schmitt et al[23] significant changes of echocardiographic parameters were detected even after administration of cumulative anthracycline doses of 100-200 mg/m2 and 200-300 mg/m2. So as in a study done by Murat Soker et al, 4 patients out of 31 had abnormal systolic cardiac function parameters, with the median cumulative doxorubicin doses of the patients with normal and abnormal echocardiographic parameters were 240 and 270 mg/m2[24].

In our study, two of the patients receivied >300mg/m2, both of them (100%) had elevated serum Troponin levels. In one of the patients, serum troponin hs was significantly elevated. In a study by Swain SM et al[25] cumulative dose of anthracyclines therapy caused 5% incidence of cardiotoxicity and is an equivalent of 400 mg/m2 of doxorubicin[25] which was similar in all groups in Cardinale D et al study (484 mg/m2, 492 mg/m2 and 499 mg/m2 in troponin-negative, Troponin-early positive and Troponin-late positive patients respectively)[26].

In the study by Murat Soker et al; all of the patients cTnI values were below the detection limit. For this

reason, they do not speculate a correlation between cTnI and doxorubicin-induced cardiotoxicity[24]. Chest X-ray is not sensitive and may not be helpful, especially in the early stages of anthracycline cardiotoxicity. In the late stages, after appearance of symptoms of congestive heart failure, nonspecific cardiomegaly or pulmonary edema may be seen[27], in our study chest X-ray showed abnormal findings in only two cases who developed symptoms, one of the cases developed features of congestive heart failure and her chest X-ray showed cardiomegaly with pleural effusion and pulmonary edema, while the other patient had only mild increase in cardiothoracic ratio.

In regard to age, in our study, there was poor relation between age of the patients and cardiotoxicity with P value 0.07, so as a study done by Al-Biltagi et al[28], as no relation was found between age of the patients and cardiotoxicity. As for gender, females were at greater risk for developing cardiotoxicity than males according to Lipshultz et al[29], which is in accordance to our study we had two cases who received high doses >300 both of them were of female gender and both of them (100%) were found to have cardiac abnormality. However Al-Biltagi et al28 did not find any relation between gender of the patients and cardiotoxicity with P- value=0.53.

Conclusions

Serum troponin TnT hs and echocardiography can be used to detect early cardiotoxicity induced by anthracycline. These results argue the use of anthracycline in children, especially when there are alternative treatments. To establish the natural history and clinical importance of cardiac abnormalities prolonged follow-up is necessary. Serial and Long term follow up is crucial for detecting early and late anthracycline induced cardiotoxicity.

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