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ORIGINAL ARTICLE

Rate of Cardiotoxicity in Childhood Acute Lymphoblastic Leukemia Treated with Daunorubicin Using Echocardiography and Troponin I

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Abstract:

Background and Aim: *Acute lymphoblastic leukemia (ALL) is the commonest malignancy in childhood. Childhood ALL Survivors have a lifelong increased risk for cardiovascular morbidity and mortality compared to the general population, mainly caused by chemotherapy with daunorubicin. The aim of the study is to detect the rate of daunorubicin induced cardiotoxicity in children with acute lymphoblastic leukemia during induction phase chemotherapy.*

Meterials & Methods : *This prospective observational study was conducted in the department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU) on 40 newly diagnosed patients of ALL aged between 1 to17.9 years who got daunorubicin during induction. Complete blood count and echocardiography were done and troponin I was measured in all patients before and after completion of induction period.*

Result: *Of the 40 patients, 8 patients (20%) had developed cardiotoxicity evidenced by reduction of left ventricular ejection fraction (LVEF) in echocardiography. Baseline LVEF was 68.80±5.98% which was then reduced to 65.32±7.07% after induction phase of chemotherapy (p=0.023). No significant alteration of troponin I was seen (P= 0.581) between baseline and after completion of induction. Total WBC count and hemoglobin had a significant difference (P<0.05) between baseline and after induction period. Male patients had a greater risk of developing cardiotoxicity than females but statistically was not significant (P=0.643). There was no significant association between age of the patients and cardiotoxicity (P=0.112).Cardiotoxicity was seen higher in patient with initial high WBC count (p=0.039). Echocardiography also reveled increased tendency of mitral regurgitation and left ventricular hypertrophy after induction phase chemotherapy.*

Conclusion: *This study showed the rate of cardiotoxicity was 20% in ALL patients treated with daunorubicin. It also found that LVEF was decreased during therapy.Echocardiography can be used to detect early cardiotoxicity induced by daunorubicin.*

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Introduction:

Acute lymphoblastic leukemia (ALL) is the commonest malignancy in childhood. It represents 25%-30% of all childhood cancers and approximately 75% of all cases of childhood leukemia.[1] The 5-year survival rate for children with ALL has greatly increased over time and is now more than 85% overall. The improved survival in childhood ALL comes at the cost of using contemporary multi-agent chemotherapy.[2] All patients with ALL receive anthracyclines, at some point during therapy, but high-risk group patients receive it from the beginning of induction therapy. While they have been established to be greatly effective in the treatment of ALL, anthracyclines have been related to myocardial toxicity, with the cumulative total dose being the best predictor of the risk.[3]

Cardiotoxicity is a well-known and potentially serious complication of anticancer therapy that can significantly impair the patient's quality of life and substantially increase health care costs. A wide range of chemotherapeutic agents are associated with cardiotoxicity include anthracyclines,

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cyclophosphamide, ifosfamide, cytarabine, cisplatin, paclitaxel, fluorouracil, and amsacrine.[4] Of these, anthracyclines (daunorubicin, doxorubicin, idarubicin, mitoxantrone, etc.) represent the greatest risk for the development of cardiotoxicity.[5]

Daunorubicin, in the anthracycline family, has been used in high-risk ALL treatment protocols during induction period. Being an important side effect of daunorubicin, cardiotoxicity may limit the efficacy of cancer therapies in the acute phase and induce the long-term sequelae, observed years after treatment completion in childhood cancer survivors.[6] Detection of cardiomyocyte damage due to daunorubicin should be done before irreversible cardiomyocyte dysfunction occurs to combat cardiotoxicity associated morbidity and mortality. Mortality related to cardiac causes is about tenfold higher among childhood cancer survivors as compared to age-matched control subjects.[7]

Measurement of left ventricular ejection fraction (LVEF) by echocardiography is frequently used to assess cardiotoxicity in patients receiving anthracyclines. The sensitivity of echocardiography for detection of LVEF in patients treated with anthracyclines is 28.6% and specificity is 94.6%. Though its sensitivity is low but used to detect cardiotoxicity because of its widespread availability, low cost and the absence of radiation exposure.[8]

There is a growing expectation for newer, non-invasive, cost-effective diagnostic tools for the early identification of patients prone to developing drug-induced cardiotoxicity. Biochemical methods using cardiac biomarkers such as troponins and brain natriuretic peptide (BNP) have emerged as sensitive tools for predicting cardiac dysfunction. Cardiac troponins are the gold standard biomarker measures in any scenario involving myocardial injury. Patients with persistent elevation of Troponin I (TnI) seem to be at particular risk of developing chemotherapy induced cardiotoxicity.[9]

So this study was supposed to show lights on early detection of cardiotoxicity during the course of treatment which may help for adjustment of chemotherapy regimens and/or the initiation of cardioprotective strategies to reduce treatment-related mortality and morbidity. Therefore,objective of the study was to detect the rate of cardiotoxicity in children with acute lymphoblastic leukemia receiving daunorubicin during induction phase chemotherapy.

Meterials & Methods:

This prospective observational study was carried out at the department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. The study period was January, 2020 to February 2021. Age between 1 to 17.9 years, newly diagnosed case of Acute Lymphoblastic Leukemia who was supposed to receive daunorubicin during induction period. Parents & guardians given consent for protocol based chemotherapy were included. Age less than 1 year and more than 18 years, children known case of congenital heart disease, Children who had sepsis or renal impairment during sample collection for biomarker, echocardiography shows baseline LVEF <60% and relapse case of ALL had been excluded from the study. Data was collected using a preformed data collection sheet (questionnaire). Demographic data regarding age, sex, socio–economic status, family history of malignancy was collected from guardian or parents. Medical data regarding initial presentation at diagnosis, treatment starting date, complication during treatment was compiled. Clinical information about pallor, hepatosplenomegaly, lymphadenopathy, Bleeding manifestation, temperature, pulse, blood pressure, respiratory rate and other general and systemic clinical parameters were noted.

Chemotherapy was given to all patients with acute lymphoblastic leukemia according to UK ALL 2003 protocol regimen-B. General supportive management like hydration, alkalinization, allopurinol, phosphate binder, oral care, anal care etc. were administered in all patients.

Patients were on regular follow up. Skin survey, oro-nasal examination, urine, stool, cannula or procedure site examination and other physical examination were done regularly on each patient. Baseline CBC, echocardiography and troponin I were done before starting chemotherapy along with other routine initial work up including bone marrow study, chest X-ray, CSF study, S. LDH, S. uric acid, S. inorganic PO4, S. electrolyte, S. calcium, S. ALT, S. Creatinine, blood grouping and Rh typing etc. Child was excluded if baseline echocardiography shows LVEF < 60% or any known case of congenital heart disease.

Afterwards, CBC, echocardiography and troponin I were assessed again after completion of induction.

Echocardiography was done by qualified physician in the Pediatric Cardiology Department in BSMMU. 2D and M-Mode echocardiography were done by GE Healthcare Ultrasound VIVID7 machine. In the setting of chemotherapy, cardiotoxicity is routinely defined as a reduction of LVEF >5 % to <55% with symptoms of HF or an asymptomatic reduction of LVEF> 10 % to a LVEF <55%.[10]

Troponin I values were done in Department of Biochemistry in BSMMU. Troponin I was measured by

Abbott Architect-Plus ci4100 automated analyzer according to the manufacturer's guidelines. In our study, values >0.08ng/ml.[11] were considered elevated and suggesting cardiac injury associated with the treatment. The patients were evaluated at baseline before induction and after completion of induction.

Statistical analyses were performed by using SPSS for windows version 22.0. p-value <0.05 and a confidence interval was set at 95% level were considered statistically significant.Chi-square test was done to measure the relationship between two qualitative variables.

Result:

Table-I

Demographic characteristics of the study subjects (n=40)

Characteristics	Frequency	Percentage
Age in years		
1-10	16	40.0
>10	24	60.0
Mean±SD	10.15±3.93	
Range	1.4-15.9	
Sex		
Male	24	60.0
Female	16	40.0
Male female ratio	1.5:1	
Diagnosis		
ALL		
T cell lineage	8	20.0
B cell lineage	32	80.0

Table II: In this study (Table I) shows majority (60%) were age group >10 years. Regarding sex (60%) were male and 40% were female. Majority (80%) was B cell lineage and 20% were T cell lineage.

Table-II

Cardiac manifestation of the study subjects (n=40)

	Before induction		After induction		P value
	No.	%	No.	%	
Chest pain					
Present	0	00	2	5.0	0.264
Absent	40	100	38	95.0	
Palpitation					
Present	2	5.0	3	7.5	0.627
Absent	38	95.0	37	92.5	
Tachycardia					
Present	2	5.0	3	7.5	0.627
Absent	38	95.0	37	92.5	

Here 5% had chest pain after induction but had no chest pain before induction. Before induction 5% had palpitation and 7.5% had after induction. Tachycardia had found 5% in before induction and 7.5% had after induction. The difference was statistically not significant before induction and after induction (P>0.05). (Table II)

Table-III

Baseline laboratory and echocardiographic findings of the study subjects

Parameter	Mean±SD	Range
WBC (cumm)	79798±64411	4500-320000
Hb (gm/dl)	7.95±1.81	4.2-12
Platelet count (cumm)	80925±6872	9000-262000
Serum LDH (U/l)	526.40±66.18	260-9341
Troponin I (ng/ml)	0.02±0.01	0-0.025
LVEF (%)	68.80±5.98	60-83

Baseline laboratory and echocardiographic findings, WBC was 79798±64411, Hb% was 7.95±1.81, platelet count was 80925±6872, serum LDH was 526.40±66.18, Troponin I was 0.02±0.01, LVEF was 68.80±5.98. (Table III)

Table-IV

Laboratory and echocardiographic findings after induction of the study subjects.

Biochemical investigation	Mean±SD	Range
WBC(cumm)	6529±2285	1000-10300
Platelet count (cumm)	98897±8826	155000-30000
Hb(gm/dl)	8.64±0.810	6.9-10.8
Troponin I(ng/ml)	0.01±0.01	0.001-0.03
LVEF (%)	65.32±7.07	78-42

Table IV shows laboratory and echocardiographic findings after induction, WBC was 6529±2285, Hb% was 8.64±0.810 platelet count was 98897±8826, Troponin I was 0.01±0.01, LVEF was 65.32±7.07.

Table-V

Prevalence of cardiotoxicity of the study subjects (n=40)

Cardiotoxicity	Frequency	Percentage (%)
Present	8	20.0
Absent	32	80.0

In this study 20% were positive and 80% were negative for cardiotoxicity (Table V).

Table-VI

Patients components of cardiotoxicity positive cases (n=8)

Case No	Age	Sex	Before induction LVEF(%)	After induction LVEF(%)	Before induction Troponin I(ng/ml)	After induction Troponin I(ng/ml)	Reduce LVEF(%)
12	14.7	Male	76	64	0.02	0.02	15.9
13	13	Female	73	60	0.02	0.01	17.8
19	13.2	Male	62	42	0.04	0.02	32
23	3.8	Male	83	64	0.01	0.02	22.9
25	15.9	Male	72	57	0.01	0.01	20.8
33	11.5	Male	70	60	0.01	0.01	14.3
35	12	Male	60	52	0.01	0.003	13.3
36	4.7	Male	80	66	0.01	0.01	17.5

Table-VIII

Comparison of investigation at baseline and after induction of the study subjects

Parameter	Baseline mean±SD	After inductionmean±SD	P value
WBC(cumm)	79798±64411	6529±2285	0.001
Platelet count (cumm)	80925±6872	98897±8826	0.460
Hb(gm/dl)	7.95±1.81	8.64±0.810	0.018
Troponin I(ng/ml)	0.02±0.01	0.01±0.01	0.581
LVEF(%)	68.80±5.98	65.32±7.07	0.023

Table VIII shows platelet count, and Troponin I were no significant difference between baseline and after induction (P>0.05). But WBC, Hb% and LVEF were significant different between baseline and after induction (P<0.05).

Table-IX

Association of WBC count and cardiotoxicity

WBC(cumm)	Positive(n=8)		Negative(n=32)		P value
	No	%	No	%	
d”100000	3	37.5	19	59.4	0.039
>100000	5	62.5	13	40.6	

Table IX shows cardiotoxicity was higher in patient with initial high WBC count and was statistically significant (P<0.05).

Discussion:

In spite of the high cure rate of childhood ALL, challenges like increase relapse rate, toxic death, and treatment-related morbidity like cardiotoxicity are important obstacles for the successful completion of treatment. Different studies are done to find out the incidence of cardiotoxicity in ALL patient treated with Daunorubicin. This study was done to evaluate the rate of cardiotoxicity in ALL patient treated with Daunorubicin during induction period.

This study shows the 60% of ALL patients fall in the age group >10 years followed by 40% in the 1-10 years age group. Maniu et al. (2018) found 71% of children were 1-10 years and 29% were >10 years. The higher percentage of >10 years age group patients in our study may be due to the inclusion of high risk ALL patients who are getting daunorubicin.[12]

In this study, there was a male predominance with a male-female ratio of 1.5:1. Male predominance in acute

lymphoblastic leukemia was also found in previously reported studies. Jessica et al. (2017) also found incidence rates of ALL higher in males.[13]

In this study, 20% of patients had cardiotoxicity. Linares et al. (2021) reported cardiotoxicity was 13.5% of patients with acute lymphoblastic leukemia.[14] Annur et al. 2021 found 21.6% of children with high risk ALL treated with daunorubicin during the induction period experienced cardiac dysfunction.[15]

This study shows after induction Troponin I did not significantly raise from baseline (P= 0.581). Similar findings were also observed by Linares et al. (2021) among high risk ALL children's who were treated with daunorubicin.[14] No significant alteration has been seen in troponin I before and after induction. Moreover, no relationship was seen between alteration of troponin I and the presence of cardiac involvement. Radu et al. (2017) found Troponin I had the same value at baseline and one hour after the first dose of doxorubicin. They also found a very significant elevation in TnI at the end of all doxorubicin doses compared to baseline levels ($p<0.0001$). They performed a Pearson correlation, between TnI resulting in a positive, but weak value, showing that the troponin level was directly proportional with the cumulative dose of doxorubicin given throughout the treatment course.[2]

Sherief et al (2013) assess the role of biomarkers in relation to anthracycline induced cardiotoxicity investigated asymptomatic survivors of childhood acute leukemia where none of the survivors had elevated troponin levels. The absence of abnormal troponin in survivors suggests that troponin does not play a role in the detection of late-onset anthracycline induced cardiotoxicity.[16]

In this study laboratory and echocardiographic findings at baseline shows total WBC count was 79798±64411 cumm, Hb was 7.95±1.81 gm/dl, platelet count was 80925±6872 cumm, serum LDH was 526.40±66.18 u/l, Troponin I was 0.02±0.01 ng/ml, LVEF was 68.80±5.98%. Platelet count, and Troponin I had no significant difference between baseline and after induction ($P>0.05$). But total WBC count, Hb, and LVEF had a significant difference between baseline and after induction ($P<0.05$). Maniu et al. (2018) found that hemoglobin was 6.58±2.50, leukocytes was 18468±30713, platelets was 67857.14± 69621.07, LDH was 662.89±927.23, and Troponin T 4.35±2.59.[12]

This study shows baseline LVEF 68.80±5.98% reduced to 65.32±7.07% after induction ($p=0.023$). These findings are similar to Shaikh et al. (2013) they found a baseline LVEF of 69±4% reduced to 62.6±9.6% ($p<0.001$) at one year after completion of anthracycline therapy.[17]

Regarding echocardiographic evaluation, it is widely accepted that children receiving cardiotoxic chemotherapeutic agents should have a baseline evaluation as well as frequent follow-ups, in order to determine subclinical cardiac ischemia (Lipshultz et al. 2012). The measurement of the echocardiographic LVEF is most widely used diagnostic method for detecting cardiotoxicity in children.[18] Generally, the cut-off value for LVEF is 60-65%. Similar cut-off values have been considered in this study. Reduction of LVEF value of 10% being considered significant for an alteration of the heart's function. A meta-analysis found that changes in myocardial structure precede changes in LVEF in exposed patients to anthracyclines, even at doses lower than those historically thought to be cardiotoxic (Thavendiranathan et al. 2014).[19]

Regarding age, in this study, there was no significant correlation between age of the patients and cardiotoxicity ($P=0.112$). Abdulqader et al. (2018) found no significant relationship between the age and cardiotoxicity.[20]

Considering gender, males had a greater risk of developing cardiotoxicity than females but statistically not significant ($P=0.643$). Linares et al. (2021) also found no relationship between gender and cardiotoxicity.

In our study echocardiographic findings at baseline also shows Mild TR 5%, Mild MR 2.5% and pulmonary hypertension 2.5%. After induction echocardiography shows mild MR 5%, mild concentric LVH 5%, mild pericardial effusion 2.5% which indicate increase tendency of MR and LVH after induction phase chemotherapy. Linares et al (2021) shows patients with high-risk leukemia had Pericardial effusion (6.3%), Valvular insufficiency (1.8%) and Pulmonary hypertension (8.0%) in echocardiographic findings and cardiotoxicity only related to pulmonary hypertension ($p=0.038$).[14] These results indicate that chemotherapy leads to increased tricuspid valve regurgitation after treatment.

We acknowledge the limitations of this study. Other investigation to detect LVEF like 3D or strain echocardiography, Doppler myocardial imaging (DMI) and Cardiac MRI were not done which may give more precise information. Biomarkers to detect cardiotoxicity like Troponin T and NT-pro BNP were not measured.

Conclusion:

This study showed the rate of cardiotoxicity was 20% in ALL patients treated with daunorubicin. It also found that

LVEF was decreased during therapy. Echocardiography can be used to detect early cardiotoxicity induced by daunorubicin.

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