EVALUATION OF DOXORUBICIN INDUCED CARDIOTOXICITY IN CHILDREN WITH ACUTE LEUKEMIA.

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ABSTRACT

Background: Acute leukemia represents the most common malignant conditions of childhood, accounting for one third of childhood cancer. Anthracyclines as Doxorubicin are highly effective chemotherapeutic agents used in acute leukemia treatment but has cardiotoxicity as major side-effect that may compromise their clinical effectiveness. **Objectives:** To identify the incidence of chronic early and late onset subclinical anthracyclines-induced cardiotoxicity in children with acute leukemia. **Patients and methods:** This prospective non-interventional study was carried out at Oncology Unit in Pediatrics Department in Zagazig University Hospitals during the period from January 2008 to December 2010. The study included 100 pediatric patients who were treated for acute leukemia and received anthracyclines in their treatment protocols, they divided into two groups (I) and (II) each contain 50 patients. We evaluated these patients using conventional echocardiography and Tissue Doppler Imaging (TDI) together with blood sampling to determine serum level of NT-PBNP and cardiac Troponin T (cTnT). **Results:** Aberration in diastolic stage of myocardial cycle in TDI study may be an early sign of cardiotoxicity as in group (**I**).The follow up dependent aggravations of subclinical cardiomyopathy is obvious in our study as detected in group (**II)**. Regarding echocardiography FS and EF were frequently abnormal in group (**I**) but in group (**II**) dilated LVEDD, thinner IVS, decreased EF, FS and increased LVPW thickness were observed in patients with subclinical cardiotoxicity.Plasma NT-pBNP was significantly elevated in 18% asymptomatic patients in group (**II**) and in 10% of patients in group (**I**).Cumulative anthracyclines dosage > 300 mg/m2 is an important risk factor to develop subclinical cardiotoxicity. Serum level of cTnT was not significantly elevated in both groups after treatment by anthracyclines. **Conclusion:** Patients who received anthracyclines should have lifelong follow-up using new highly sensitive non-invasive methods for early detection of subclinical cardio toxicity.

Keywords: acute leukemia, cardiotoxicity, anthracyclines.

INTRODUCTION

Acute leukemia represents the most common malignant conditions of childhood, accounting for one third of childhood cancer [(1)].

The biological heterogeneity of childhood leukemia is well documented, with the major morphological types being Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML). ALL is the predominant leukemia in childhood which account for 75 % of all cases while AML accounts for around 17 % of cases [(2)].

Almost universally fatal 50 years ago, acute leukemia now has an overall survival of over 80% as regard Acute Lymphoblastic Leukemia (ALL), and the prognosis of children with Acute Myeloid Leukemia (AML) has improved greatly over the past 3 decades, with overall survival rate of about 50-60% now reported. This improvement in over all survival has been due to the development of new chemotherapeutic agents together with enhanced support services [(3)].

Unfortunately, the improvement in prognosis has been accompanied by a significant increase in morbidity and occasionally mortality. A considerable price has been paid in terms of side effects associated with intensive anticancer treatment [(4)].

Anthracyclines are highly effective chemotherapeutic agents used to treat a wide variety of common malignancies, including, acute leukemia, lymphoma, sarcoma of soft tissue and bone, Wilm's

tumor, neuroblastoma and hepatoblastoma.[5]But cardiotoxicity is growing problem and a common complication of anthracyclines that may compromise their clinical effectiveness, oncologic prognosis, and leave its impact on the patient's survival and quality of life [6].

The prognosis of cardiomyopathy, once developed, is grave, and it is difficult to predict which individuals will develop heart failure on a case-by-case basis.[7].The cardiotoxicity of anthracyclines appear to be distinct from its therapeutic mechanism and has been attributed to multiple effects on cardiac myocytes, including apoptosis, alterations of iron homeostasis and mitochondrial dysfunction [8].

Anthracyclines cardiotoxicity can be classified as acute and chronic. Acute cardiotoxicity is independent on the anthracycline dose, usually minor and reversible, ranging from asymptomatic ECG changes to rare cases of acute myocarditis. ([9].

While chronic cardiotoxicity may occur early or late onset and typically manifest months or years after chemotherapy and can lead to cardiomyopathy with a poor prognosis of the affected patients [10].

And in addition to clinical cardiotoxicity, manifesting itself as CHF, subclinical cardiotoxicity has been reported. [11]

The early identification of patients at risk for cardiotoxicity is a primary goal for both cardiologists and oncologists, allowing for the planning of personalized antineoplastic therapeutic strategies, the support of cardiac function, and the monitoring of the progression of cardiac damage [12].

A number of techniques are available including the use of imaging modalities and specific markers of cardiac injury. Echocardiography is widely used non invasive methods of monitoring the cardiotoxicity of cancer therapy and provide wide spectrum of information on cardiac morphology and function [13].

Tissue Doppler imaging is a new, sensitive, noninvasive echocardiography method that records velocity of tissue motion within the myocardium and appears to offer significant advantage over the traditional technique [14].

Biomarkers of cardiac damage are alternative method of monitoring. Cardiac troponins (I and T) are specific markers of myocardial damage in myocardial infarction and myocarditis. Cardiac injury can also be determined by natriuretic peptides which are released from the atria (atria natriuretic peptides) and the left ventricle, Brain Natriuretic Peptides (BNP) in response to circulating volume and intracardiac pressures [15].

The chosen method should be highly sensitive, specific, and noninvasive and one with which the center is familiar. ([16].

PATIENTS AND METHODS

This prospective non-interventional study was carried out at Oncology Unit in Pediatrics Department in Zagazig University Hospitals during the period from January 2008 to December 2010.informed consents were taken from the patients or their parents.

In these patients we aimed to identify the incidence of early and late onset chronic subclinical anthracyclines-induced cardiotoxicity which occurs in patients treated for acute leukemia.

The study included 100 patients, divided into two groups, each consists of 50 patients. Group (I) is evaluated for chronic early onset subclinical cardiotoxicity. So, patients evaluated at baseline and at regular interval within one year after starting treatment by anthracyclines. Group (II) is evaluated for chronic late onset subclinical cardiotoxicity. So, patients are evaluated at the baseline and after one or more years of finishing treatment by anthracyclines.

Inclusion criteria:

1- Acute myeloid leukemia patients, high-risk acute lymphoblastic leukemia patients and acute leukemia relapse patients.

2- Patients at time of examination and evaluation should have no signs or symptoms of cardiac impairment.
3- No history of congenital or acquired heart disease.
4- Normal liver and kidney function tests.
5- The patients at time of evaluation should have stable general condition.

Methods of evaluation:

For all patients, demographic data including age, sex, weight, surface area of body, diagnosis, all laboratory workup done for the patients and clinical history. Cumulative dose of anthracyclines were calculated for each patient according to his surface area.

Methods of evaluation for each patient were:-

(1)Echocardiography method: Conventional echocardiography was performed at Pediatric Cardiology Unit, Pediatric Department, at Zagazig University Hospitals by the same operator (AA). For all patients, standard measurements were: Left Ventricular Posterior Wall thickness at end-diastole (LVPW), the thickness of the Interventricular Septum at end-diastole (IVS), the Left Ventricular Dimensions at End-Systole (LVESD), and End-Diastole (LVEDD), Ejection Fraction (EF) estimated by cube method and Fraction Shortening (SF). All measurements were made according to echocardiography and normal values of LVPW, IVS, LVEDS and LVEDD were taken from standard tables according to ages and body surface area. An EF of less than 55% was considered abnormal and SF of less than 29% was considered abnormal.

(1) Tissue Doppler Imaging:

Tissue Doppler imaging were obtained according to the methods described by **Kapusta et al. (2000)**, in the parasternal long-axis view measurements of peak myocardial velocities were made guided by color-coded tissue Doppler imaging. Peak myocardial velocity during systole (S), early diastole (De) and late diastole (Da) were measured at the Right and Left ventricular sides of Interventricular Septum (IVSR and IVSL) respectively and the endocardial (endo) and epicedial (epi) side of Left Ventricular Posterior Wall (LVPW). Transmyocardial velocity gradients were defined as the velocity difference between the left and right sides o IVS and between the endocardial and epicardial sides of the LVPW. Transmyocardial gradient were calculated for each cardiac cycle phase (S, De and Da) separately, in the apical four-chamber view Doppler velocity-time sonography were recorded using single-gated TDI. Peak longitudinal myocardial velocities were assessed during systole (S), early diastole (De) and late diastole (Da) within basal, middle and apical parts of the Right Ventricular Wall (RVW) and Left Ventricular Wall (LVW). Ratios of peak velocities in early and late diastole (De/Da) and early diastole and systole (De/S) were calculated for all TDI measurements.

(2) Serum level of (cTnT):

Heparin plasma samples for cTnT were obtained and the samples were centrifuged immediately and were stored at -20 C until further analysis .Troponin T was measured using the 3rd generation Elecsys Troponin T STAT immunoassay, standardized with human recombinant cTnT. Abnormal level was defined as a cTnT more than 0.010 ng/ml. the technician who performed the assay was blinded to both the clinical and echocardiography results.

(3) Serum level of NT-pBNP:

Blood samples (3 ml) were collected in K-EDTA tubes within 3 hours of the echocardiography and tissue Doppler imaging and were centrifuged immediately at 3,500 rpm for 10 minutes. Platelet-free plasma was stored at -20°C. NT-PBNP was performed using ELISA technology. For normal values of children, we used the age dependent reference values by **Thomas S. et al (2002.)** Also the technician who performed the assay was blinded to both the clinical and echocardiography results.

Statistical analysis:

Data were entered checked and analyzed using Epi-Info version 6 and SPP for Windows version 8. Data were summarized using the arithmetic mean, the Standard Deviation (SD), median, screening test, student t test, X^2, Mann Whitney-U test and level significance.

RESULTS

Table (1) shows the characteristics of the studied group (**I**) according to age, sex, weight, surface area and diagnosis.

Table (2) shows the characteristics of the studied group (**II**) according to age, sex, weight, surface area and diagnosis.

Table (3) shows that: with more increase of the duration of follow up there was significant increase of the left ventricular diameter at end systole and end diastole in group (**II**)

Table (4) shows that: in group (**II**) the patients who show abnormalities in TDI parameters were younger at diagnosis, more duration of follow up and received more cumulative doses of anthracyclines than the other patients who showed normal serum levels of NT-PNBP. The sex and the age at follow up were not significantly different.

Table (5) shows that in group (**II**) patients who received cumulative doses more than 300 mg/m^2 were associated with increased diameter of left ventricle at end diastole and end systole (LVEDS) & (LVEDD) but there was no significant change in other echocardiography parameter.

Table (6) shows that: in group (**II**) patients who show abnormalities in TDI parameters had more decrease in ejection fraction (EF), fractional shortening (FS) and significant increase of the diameter of left ventricle at end diastole (LVEDD).

Table (7) shows dilated LVEDD and LVESDD especially in group II and thinner IVS in both groups, but more common in group II.

Table (8) patients who show abnormalities in TDI parameters had more decrease in ejection fraction (EF), fractional shortening (FS) and significant increase of the diameter of left ventricle at end diastole (LVEDD) in group (I).

Table (9) shows that in group (**II**) the patients who show abnormal serum level of NT-PBNP.were younger at diagnosis, more duration of follow up and received more cumulative doses of anthracyclines than the other patients who showed normal serum levels of NT-PNBP. The sex and the age were not significantly different

Table (1): **Characteristic of Group** (I): 50 patients.

Male Gender	23(64%)
Median age at study	6.21±3.65(1.3-13)
Median CAD mg/m^2	147±53(70-297)
CAD<150 mg/m^2	36(72%)
CAD<150-300 mg/m^2	14(28%)
CAD>300 mg/m^2	0(0%)
Diagnosis	
ALL	32(64%)
AML	18(36%)

Table (2): Characteristic of Group (II): 50 patients.

Male Gender	30(60%)
Median age at diagnosis in years	8.4±3.46(3-15)
Median follow up years	3.75±2.25(1.5-6)
Median age at evaluation in years	11.63±2.17(8-16)
CAD<150 mg/m^2	0(0%)
CAD<150-300 mg/m^2	18(36%)
CAD>300 mg/m^2	32(64%)
Diagnosis.	
ALL	15(30%)
AML	10(20%)
Leukemia relapse	25 (50%)

CAD: cumulative anthracyclines doses,

Table (3): Echocardiography parameters in relation to duration of follow-up in group (II).

No of patients. Mean±SD	Abnormal N=8 (16%)	Normal N=42 (84%)	P-value
EF	6(12%) 3.5±0.54	44(88%) 2.94±1.96	0.384
FS	6(12%) 3.5±0.54	44(88%) 2.9±1.46	0.364
IVSD	5(10%) 3.0±0.00	45(90%) 3.011±1.47	0.978
LVPW thickness.	4(8%) 3.5±0.54	46(88%) 2.94±1.96	0.786
LVEDS	5(10%) 5.076±0.54	45(90%) 2.72±1.13	0.001
LVEDD	8(16%) 5.0±0.921	42(84%) 2.63±1.12	0.000*

LVEDD: Left Ventricle End Diastole Diameter, LVEDS: Left Ventricle End Systolic Diameter, EF: Ejection Fraction, FS: Fractional Shortening, IVSD: Inter-Ventricular Septum Diameter, LVPW thickness: Left Ventricular Posterior Wall thickness**.**

Echocardiography parameters in relation to duration of follow-up In group (II)

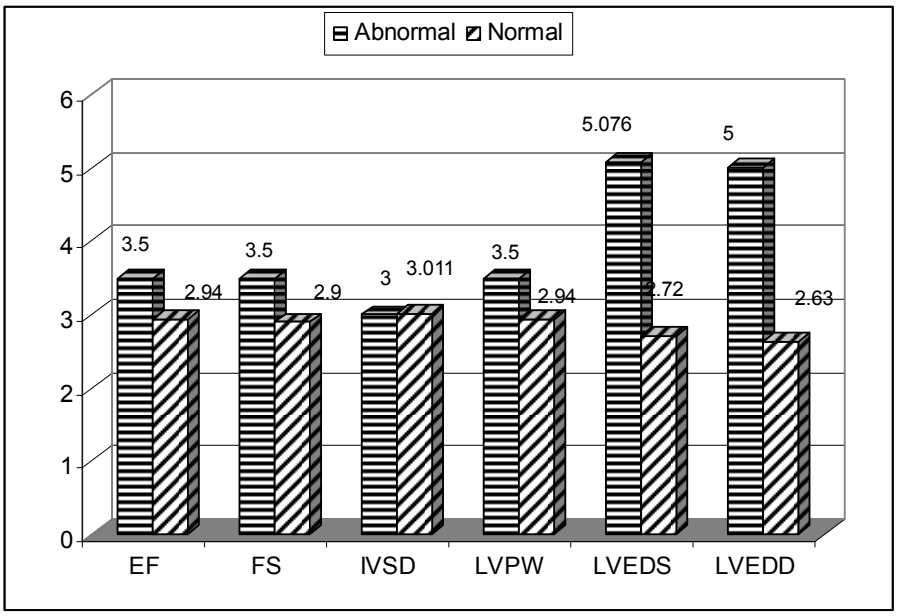

Table (4): Patients who show abnormality in TDI parameters and Risk factors in group (II)

	Abnormal N =13 (26%)	Normal N=37 (74%)	P-value
Age at diagnoses.	5.0±2.08	6.4±1.84	0.027*
Ag at evaluation.	11.69±2.05	11.6±2.24	0.906
Duration of follow-up	4.23±1.23	2.58±1.18	.000**
Cumulative Dose	469.69±118.89	338.76±76.54	.000**
Sex	22.96 (sum of rank 425.5)	32.73 (sum of rank 849.5)	0.016*
	Male 14=37.8%	Male 10=76.9%	0.013*
	Female 23=62.2%	Female 3=23.1%	

Table (5): Relation of Cumulative anthracyclines Doses in (mg/m^2) and ECHO parameters in group (II).

	<300 mg N=19 (38%)	> 300mg N=31 (63%)	P-value
EF	67.37±2.79	62.61±6.54	0.089
FS	34.4±2.63	33.19±4.84	0.326
IVSD	5.46±1.22	5.20±1.006	0.430
LVPW	5.74±0.45	5.68±1.14	.829
LVEDS	25.89±2.31	29.23±3.23	**0.000
LVEDD	37.37±0.955	41.71±6.29	**0.005

Table (6): Relation between patients who show abnormalities in TDI parameter and echocardiography parameter in group (II)

	Abnormal N=13 (26%)	Normal N=37 (74%)	P-value
EF	60.0±7.62	67.48±3.09	0.000**
FS	29.76±4.36	35.05±3.58	0.000**
IVSD	5.11±1.17	5.37±1.06	.469
LVPW	6.0±0.71	5.59±0.98	0.180
LVEDS	29.69±4.26	27.35±2.73	.027*
LVEDD	45.53±7.91	38.13±2.016	0.000**

Table (7): Serum level of NT-PBNP In relation ECHO parameters in group (I).

	Abnormal N=5 (10%)	Normal N=45 (90%)	P-value
EF	55.4±3.3	68.42±3.2	0.00**
FS	40.0±2.73	37.6±3.67	0.164
IVSD	5.2±1.6	5.5±1.1	0.482
LVPW	5.8±1.09	5.48±1.03	0.529
LVEDS	24.0±0	26±2.4	0.025*
LVEDD	38±0	36.33±3.3	0.278

Table (8): Relation between patients who show abnormalities in TDI parameter and echocardiography parameter in group (I)

	Abnormal N=13 (26%)	Normal N=37 (74%)	P-value
EF	60.0±7.62	67.48±3.09	0.000**
FS	29.76±4.36	35.05±3.58	0.000**
IVSD	5.11±1.17	5.37±1.06	.469
LVPW	6.0±0.71	5.59±0.98	0.180
LVEDS	29.69±4.26	27.35±2.73	.027*
LVEDD	45.53±7.91	38.13±2.016	0.000**

Patients who show abnormalities in TDI parameters and echocardiography parameters in group (I).

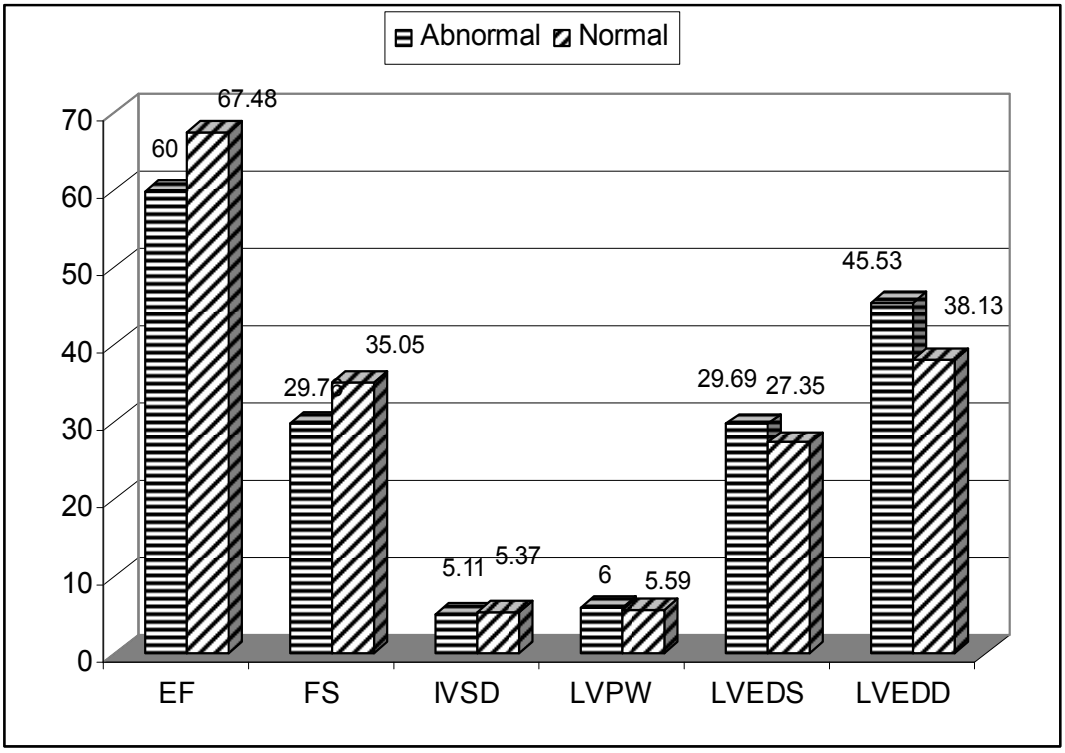

Table (9): Levels of NT-PBNP and Risk factors in group (II).

	Abnormal N=10 (20%)	Normal N=40 (80%)	P-value
Age at diagnosis	4.7±2.3	6.3±51.7	0.016*
Age at follow up	11.9±2.3	11.5 ±2.16	0.665
Duration of follow	4.6±1.17	2.6±1.41	0.000**
CAD	484.60±133.3	344.5±76.6	0.000**
Sex (rank) Manwhitney	31.0 (sum of rank 310)	24.12 (sum of rank 965)	0.189
Sex (chi-square)	Male=17(42.5%)	Male=7(70.0%)	0.123
	Female=23(57.5%)	Female=3(30.0%)	

DISCUSSION

In this prospective non-interventional study, we are evaluating two groups of survivors of acute leukemia children for chronic subclinical anthracyclines-induced cardiotoxicity which may occurs within one year of treatment (chronic early onset subclinical cardiotoxicity in group ((I) and that which may occurs one year or more after treatment (chronic late-onset subclinical cardiotoxicity) in group (II) this is was done using conventional echocardiography, Tissue Doppler Imaging (TDI), serum level of cardiac Troponin T (cTnT), and serum level of NT-probrain Natriuretic Peptide (NT-proBNP).

Our results came as follow: In group (I), we found that: 2 patients out of 50 (4%) showed chronic early onset anthracyclines induced subclinical cardiotoxicity in the form of decrease in Ejection Fraction (EF) below 55% in 2 patients, Fractional Shortening (FS) below 29% in 2 patients also. But the other echocardiography parameters as IVS, LVPW thickness, LVEDD, and LVESD, were not affected, and this was when compared with normal values for age,sex and BSA. Evaluation by Tissue Doppler

Imaging showed that 7 patients out of 50 (14%) showed myocardial damage in the form of significant aberrations in peak myocardial velocities and in ratios between velocities in early and late diastole (De/Da) and early diastole and systole (De/S). In these patients we found that reduced peak myocardial velocities in early diastole together with increased peak velocities in late diastole and decreased ratios between early and late diastolic velocities points to diastolic dysfunction with impaired capacity to fill and maintain stroke volume (decrease in De) without compensatory increase in atrial filling pressure(increased Da), so diastolic dysfunction is a prominent feature of these patients which may precede systolic dysfunction .Abnormal myocardial velocities were found in myocardial structure (RVW, IVS and LVPW) and in cardiac cycles (systole, early diastole and late diastole) but significant aberrations were noticed in early diastolic stage of cardiac cycle in cardiac structures that appeared normal by echocardiography method. Those who received cumulative doses of anthracyclines more than 150 mg/m2 are more liable to be affected. Serum level of cardiac troponin T (cTnT) were not elevated in these patients (less than 0.001 ng/ml) but serum level of NT-pBNP was significantly elevated after treatment in 4 patients out of 50 (8%) who had received anthracyclines with values (1085.5±112.5 fmol /ml) as mean ± SD and range (973-2298 fmol/ml) (p value < 0.001). Also serum levels of NT-PBNP values were significantly elevated in patients who showed cardiotoxicity detected by aberrations in TDI parameters with values (793.86±470.53fmol /ml) as mean ± SD after treatment.These results were in consistent with the results of **Ursula et al.**[18] who reported anthracyclines-induced subclinical cardiotoxicity in 24 out of 885 AML patients evaluated by echocardiography; 9 of them with SF of 20%-30% and 11 patients with SF of 25%-30% and four with temporarily decrease SF more than 10% compared to baseline.

Also, our results consistent with the results of **Broeyer et al.** [19] who reported that 21 patients who had no past cardiac problem and completed 3 courses of anthracyclines treatment and evaluated within 6 months later showed marked elevation of NT-proBNP of 277% higher in comparison to healthy volunteers but he found that cTnT concentration were below level of detection in most cases and not further analyzed for this reason. also consistent with the result of **Bryant et al.**[20] who studied 15 adult patients with AML with serial measurement of NT-proBNP, cTnT and CK-MB together with echocardiography evaluation of these patients at baseline and after each anthracyclines infusion and one month after completion of induction chemotherapy, he found that sign of echocardiography dysfunction was found in 2 patients who were asymptomatic in the form of decrease in EF below 60% in comparison to control group after one moth of induction, he also found that in all patients; plasma cTnT and CK-MB mass concentration was within the reference range after the induction therapy and the differences were not statistically significant, he also found that NT-proBNP in most patients the second and third infusion of anthracyclines were associated with increased markedly and the level after 4 weeks were not significantly different from the baseline but in one patients NT-proBNP values were increasing after each anthracyclines infusion and with 14 days, he developed congestive heart failure due to left ventricular diastolic dysfunction by Echocardiography. So, NT-proBNP is a promising early marker and predictor of this complication.

But, our results is in conflict with the study carried out by **Daniela and Maria**[21] who reported that patients without cTnT elevation after chemotherapy showed no significant reduction of LVEF, while patients who show elevations of cTnT was

consistent with greater cardiac impairment in the form of decrease in LVEF.

Also, our results came in contrast to randomized controlled study carried out by **Lipchultz et al.** [22] who found that patients who had been treated with moderate dose doxorubicin (or total cumulative dose 300 mg/m2) alone were significantly more likely to have elevated cTnT levels than those treated with dexarazoxan and doxorubicin, while no significant echocardiography indices of left ventricular performance between the groups were found.

In group((II) we found that patients out of 50 (16%) showed chronic late onset anthracyclines induced subclinical cardiotoxicity in the form of decrease in EF(< 55%) in 6 patients decrease in SF(< 29%) in decreased in 4 patients, LVESD increased in in 4 patients and increase in LVEDD in 8 patients .So EF was the most frequent Echocardiography parameter to be abnormal followed by FS, LVEDD and LVESD, this was in comparison with normal values for age and BSA .So as a group these patients had measurable signs of cardiac dysfunction with significant aberrations of nearly all of standard M-mode echocardiography parameters . Evaluation by Tissue Doppler Imaging showed that 13 patients out of 50 (26%) showed global myocardial damage in the form of significant aberrations in peak myocardial velocities and in ratios between velocities in early and late diastole (De/Da) and early diastole and systole (De/S). Abnormal myocardial velocities were found in all myocardial structure (RVW, IVS and LVPW) and in all cardiac cycles (systole, early and late diastole). Patients who received cumulative doses of anthracyclines more than 300 mg/m^2 are more liable to be affected as cardiotoxicity occurred in 2 patients who had received cumulative doses (<300 mg/m^2) and in 11 patients who received cumulative doses (>300 mg/m^2) . So, there was increase in incidence of cardiotoxicity as the cumulative doses of anthracyclines increase (p value < 0.001).Serum level of NT-pBNP. were higher than reference ranges for age in 9 asymptomatic patients out of 50 (18%) with values (1511.6±668.5fmol/ml) (843-2180 fmol/ml)after treatment by serum levels of cTnT were within normal (0.014±0.01)(0-0.004)ng/ml) as (mean±SD) (range).with (p value < 0.001) . Also NT-pBNP values were significantly elevated in patients who showed aberrations in TDI parameters with values of (1127.7±689.91) as (mean±SD) and (p value < 0.001). And also high in patients who had multiple abnormal echocardiography parameters.The result of multivariate regression analysis showed that age is an independent risk factor for cardiotoxicity in the form of decrease EF, FS and thinner IVS (p value < 0.001). But cumulative dose was dependent and most important risk factor for cardiotoxicity in the form of decrease in EF and FS (p value < 0.001) in inverse relation to cumulative doses. Also we found that the duration of follow up is in direct relation with cardiotoxicity, as the incidence of cardiotoxicity increased markedly with increase the duration of follow up. These results were consistent with the results of **Mathias et al.**[23] who studied a cohort of 63 ALL survivors and received moderate cumulative dose of anthracyclines (below 300 mg/m^2), none had cardiopulmonary symptoms .and reported 14% (9/63) of patients had measurable signs of cardiac dysfunction with significant aberrations of all standard M-mode parameters and TDI data demonstrated signs of global myocardial damage. He also reported that myocardial damage may worsen with time.

Also, our results come consistent with the results of **Elbl et al.**[24] who reported that: in study of 55 adult patients treated by doxorubicin and in long term remission after hematological malignancies he showed that EF of 5 patients (9%) decreased below 50% and although EF of another 11 patients (20%) were within the physiological range but it decreased by more than 10% as compared by their

pretreatment EF value. Also, he reported that there was impaired cardiac function as measured by Doppler parameter of systolic and diastolic function in 20 patients (36%) but he found that BNP values were high only in patients with EF of less than 50% and show signs of heart failure so BNP has negative predictive value to exclude subclinical damage to the myocardium as a result of treatment by Doxorubicin.

Also, our results were consistent with the results of **L'Ecuyer et al.** [25] who studied 63 children completed treatment by anthracyclines at least one year earlier, he found cardiac dysfunction in 26 patients (41%) as measured by different echocardiography parameter and he found that mean BNP plasma levels were in the subset of abnormal cardiac function were significantly higher than normal.

Also our results were consistent with the results of **Lessene et al.** [26] who found that there were no correlation between serum cTnT and systolic and diastolic cardiac dysfunction which were detected in 9 out of 24 children (37%) who received high cumulative doses of Doxorubicin by two-dimensional M-mode and Doppler echocardiography.

Also, our results came consistent with the results of **Lipchultz et al.**[22] who found that in cross-sectional study, the cardiac abnormalities in the form of reduction of left ventricular fractional shortening after doxorubicin therapy and that reduction was related to cumulative doses of doxorubicin and he found also that with there was progressive reduction of fractional shortening with follow up over time.

But, our results came in contrast to **Wilson et al.**[27] who reported that in a pilot study data do not support routine biomarker screening to predict subsequent development of doxorubicin-induced cardiotoxicity.

CONCLUSION

- It is important that patients who received anthracyclines should have life long follow-up
- TDI appears to be interesting and sensitive method of surveillance for the growing number of acute leukemia survivors as it may lead to earlier detection of cardiotoxicity induced by anthracyclines as the aberrations in TDI parameters were detected in structures that appeared normal by M-mode echocardiography.
- Plasma NT-pBNP was significantly elevated in patients who suffered from early and late onset anthracyclines-induced cardiotoxicity and so measurement of NT-pBNP could be used as a sensitive cardiac biomarker in monitoring of anthracyclines related cardiotoxicity.

REFERENCES

1- Adelman, A.S., Groves, F.D. and O'Rourke, K. et al.: Residential mobility and risk of childhood acute lymphoblastic leukemia: An ecological study. Brit J Cancer 2007; 97(1): 140-4.

2- Annelies M.C., Mavinkurve-Groothuis, Jacqueline GL., et al.Abnormal NT-pro-BNP.Levels in Asymptomatic Long-Term Survivors of Childhood Cancer Treated with Anthracyclines. Pediatr Blood Cancer 2009; 52:631-636.

3- Jansen MW, Corral L, van der Velden VH, et al.: Immunobiological diversity in infant acute lymphoblastic leukemia is related to the occurrence and type of MLL gene rearrangement. Leukemia 2007; 21:633-41.

4- Simon NB and Josef VH: Childhood Leukaemia. Symposium Haematology. Pediatric and Child Health 2009; 19:8; 345-350.

5- Orkin S, Fisher D, Look AT, et al.: Nathan and Oski's hematology of infancy and childhood. Philadelphia: WB Saunders 2008.

6- Rob P, William L, Carroll: Biology and Treatment of Acute Lymphoblastic leukemia. Hematology and Oncology Clinic of N Am 2010; 24; 1-18.

7- Roman, E.; Simpson, J. and Ansell, P. et al.: UK Childhood Cancer Study Investigators. Prenatal and reproductive factors: A report and hematological malignancies from the UKCCS. Euro J Cancer 2005; 41(5): 749-59.

8- Jeffrey ER, Brenda G and Franklin OS: Acute Myeloid Leukemia. Haematol Oncol Clin N Am 2010; 24: 35-63.
9- Richard S., Vander H., and Thomas JL.: Molecular basis of anthracycline-induced cardiotoxicity. Heart Metab 2007; 35: 1-4.
10- Rose, S.R.; Schreiber, R.E. and Kearney, N.S. et al.: Hypothalamic dysfunction after chemotherapy. J Pediatr Endocrinol Metab 2004; 17(1): 55-66.
11- Pudil R, Horacek JM, Horvkova J, et al.: Anthracyclines therapy can induce very early increase in QT dispersion and QTc prolongation.Leuk Res 2008; 32: 998-9.
12- Pui, C.H.; Relling, M.V. and Downing, J.R.: Acute lymphoblastic leukemia. New Engl J Med 2004; 350(15): 1535-48.
13- Thomas S.,Sonke M., Stephanie L.,et al.: plasma concentration of N-Terminal ProBrain Natriuertic Peptide in Control Children From the Neonatal to Adolescent Period and in Children with Congestive Heart Failure. PEDIATRICS 2002;Vol.110 -No.6
14- Kay KS, Cluadia L, Olle B, et al.: positive and negative consequences of childhood cancer influencing the lives of young adults. European Journal of Oncology Nursing 2009; 13; 164-170.
15- Jones LW, Haykowsky MJ, Swartz JJ et al.: Early breast Cancer: therapy and cardiovascular injury.J Am Cardiol 2007; 50: 1435-1441.
16- Adnan KH, Tirath G, Tielan F, et al.: Utility of TDI in patient with acute myocardial infarction complicated by cardiogenic shock. Cardiovascular Ultrasound 2006, 6: 11.
17- Aplan, P.D.; Jones, C.A. and Chervinsky, D.S. et al.: A gene product lacking the transactivation domain induces bony abnormalities and cooperates with LMO_1 to generate T-cell malignancies in transgenic mice. Emr J 1997; 16(9): 2408-19.
18- Zuppinger C, Timolati F and Suter TM: path physiology and diagnosis of cancer drug induced cardiomyopathy.Cardiovasc Toxicol 2007; 7: 61-66.
19- Ursula C., Sylke D., Martin Z., et al.: Longitudinal Evaluation of Eearly and Late Anthracyclines Cardiotoxicity in Children with AML. Pediatr Blood Cancer 2007; 48: 651-662.
20- Broeyer J., Osnanta S., RitsemaVan Eck H., et al.: Evaluation of biomarker for cardiotoxicity of anthracyclin-based chemotherapy. J Cancer Res Clin Oncol 2008; 134(9): 691-698.
21- Bryant J., Picot J., Baxter L., et al.: Use of cardiac marker to assess the tixic effects of anthracyclines given to children with cancer: A systemic review.European Journal Of Cancer 2007; 1959-1966.
22- Lipchultz SE., Lipsitze SR., Sallan SE., et al.: Chronic progressive cardiac dysfunction years after dixirubicin therapy for childhood acute lyphoblastic leukaemia. J C O 2005; 23(12):2629-36.
23- Mathias R., Niels L.T., and Henrik O.: Late Cardiac Effects of A nthracyclines Containing Therapy for Childhood Acute Lyphoblastic Leukaemia .Pediatr Blood Cancer 2007; 48: 663-667.
24- Elbl L., Vasova I., Navratil M., et al.: Comparisons of plasmatic levels of B-natriuretic peptide with echocardiographic indicators of left ventricular function after doxorubicin therapy. Vnitr Lek 2006; 52(6): 563-70.
25- L'Ecuyer, T.; Sanjeev, S. and Thomas, R. et al.: DNA damage is an early event in doxorubicin-induced cardiomyocyte death. Am J Physiol Heart Circ Physiol 2006; 291: H1273-H1280.
26- Lessene, G.; Czabotar, P.E. and Colman, P.M.: BCL-2 family antagonists for cancer therapy. Nat Rev Drug Discov 2008; 7(12): 989-1000.
27- Wilson T, Rohit B, Kevin S, et al.: Is there a role in routine Biomarker screening for cardio toxicity in patients receiving Doxorubicin chemotherapy? Pilot Observation. The 10th annual scientific meeting, Haematology and Oncology, Cleveland Clinic, Cleveland, OH. 2009.

الملخص العربى

مقدمة:

يعتبر سرطان الدم الحاد هو أشهر الأمراض السرطانية فى الأطفال حيث يمثل ثلث هذه الأمراض، ويتميز بالتغايرية البيولوجية، مع وجود أنواع مورفولوجية رئيسية، وهى سرطان الدم الحاد الليمفاوى ويشكل 75% من الحالات، وسرطان الدم الحاد النخاعى ويشكل من 17% إلى 20% من الحالات.

فى الماضى كان سرطان الدم الحاد يعتبر من الأمراض المميتة، ولكن فى الوقت الحاضر زاد معدل الشفاء بنسبة تصل إلى 80% فى مرضى سرطان الدم الحاد الليمفاوى وتحسن معدل الشفاء فى مرضى سرطان الدم الحاد النخاعى إلى 60%، وكان هذا نتيجة الاستخدام الحديث لمجموعات من العلاج الكيماوى مع تقدم الرعاية الطبية للمرضى.

لكن لسوء الحظ، صاحب هذا التحسن فى نسبة الشفاء زيادة فى ظهور أعراض جانبية للعلاج الكيماوى وأحياناً الوفاة بعد فترة من تمام الشفاء وكان هذا ثمن لابد من دفعه.

تعتبر مركبات الإنتراسيكلين من مضادات السرطان الفعالة فى علاج سرطان الدم الحاد، سرطان الغدد الليمفاوية، ساركوما الأنسجة الليفية، ورم ولمز، الورم الأرومى العصبى والورم الأرومى الكبدى واستخدامها فى العلاج أحدث تحسن مطرد فى معدل الشفاء.

ولكن وهن عضلة القلب الناتج عن العلاج بهذه المركبات يعتبر أكبر الأعراض الجانبية ويقف حجر عثرة فى الفاعلية الإكلينيكية، ويبقى تأثيره السيء على المريض حتى بعد تمام الشفاء من السرطان. بالشفاء من السرطان هذه المشكلة الخطيرة فى تزايد مستمر حيث أن 50% من الأطفال الذين نعموا قد تم علاجهم بمركبات الإنتراسيكلين فى خطط العلاج الكيماوى وعادةً ما تحدث عند التعرض لجرعات تراكمية كبيرة من مركبات الإنتراسيكلين.

لقد وجد أن الآلية التى تحدث بها سمية عضلة القلب تختلف عن الآلية التى تحدث بها هذه المركبات تأثيرها العلاجى وغالباً ما تكون بسبب تغيرات مختلفة فى خلايا عضلة القلب، تغير توازن الحديد فى الجسم وخلل فى وظائف الميتوكوندريا.

السمية القلبية تحدث إما بطريقة حادة او مزمنه وهي اما مبكرة أو متأخرة الحدوث. وتظهر فى شكل إما فشل فى عضلة القلب أو تحدث دون أعراض إكلينيكية .

السمية الحادة لا تعتمد على الجرعة التراكمية لمركبات الإنتراسيكلين وتكون غير خطيرة ويزول تأثيرهاً سريعاً.

أما السمية المزمنه المبكرة أو المتأخرة الحدوث تظهر أعراضها فى خلال شهور أو سنوات بعد العلاج الكيماوى.

مما سبق نستنتج أن الاكتشاف المبكر للمرضى الذين هم عرضة للسمية القلبية هو الهدف الأساسى للطرق البحثية، وهذا يسمح بوضع خطط علاج كيماوى مناسبة لكل مريض، ورصد أى تلف فى عضلة القلب مبكراً.

هناك عدة طرق يمكن استخدامها للاكتشاف المبكر للسمية التى تحدث لعضلة القلب نتيجة العلاج بمركبات الأنثراسيكلين، منها بالأشعة فوق الصوتية التقليدية على عضلة القلب، تصوير أنسجة القلب بأشعة الدوبلر أو قياس المؤشرات البيولوجية الخاصة بعضلة القلب مثل مادة التروبونين تى ومادة برو بى إن بى مصل الدم.

الهدف من الدراسة:-

تقييم تلف عضلة القلب الناتج عن استخدام عقار الأنثراسيكلين فى الأطفال المصابين باللوكيميا الحادة باستخدام المؤشرات البيولوجية لتلف عضلة القلب كمادة التروبونين تى والبرو بى إن بى ومقارنتها بالأشعة فوق الصوتية التقليدية على القلب وتصوير أنسجة القلب بأشعة الدوبلر.

المرضى وطرق البحث:-

تمت هذه الدراسة فى وحدة الأورام التابعة لقسم الأطفال فى مستشفيات جامعة الزقازيق فى الفترة من يناير 2008 إلى ديسمبر 2010. شملت الدراسة مائة مريض من الأطفال الذين يعالجون من سرطان الدم الحاد الليمفاوى أو النخاعى أو انتكاسة سرطان الدم الحاد، فى مراحل مختلفة من العلاج الكيماوى الذى يحتوى على مركبات الأنثراسيكلين. تم تقسيم المرضى إلى مجموعتين كل تشمل خمسين مريضاً.

مجموعه(1): يتم تقييم المرضى لمعرفة سمية عضلة القلب الناتجة عن العلاج بعقار الأنثراسيكلين المزمنه المبكرة الحدوث فى مرحلة ما قبل الظهور الإكلينيكى ولذلك يتم التقييم قبل بداية العلاج ثم بعد ذلك فى خلال أقل من سنة من بداية العلاج.

مجموعه (2): يتم تقييم المرضى فيها لمعرفة السمية المزمنه المتأخرة الحدوث ولذلك يتم التقييم قبل بداية العلاج وبعد سنة أو أكثر من بداية العلاج.

كل المرضى يتم أخذ تاريخ مرضى مفصل منهم ويخضعون للفحص الإكلينيكى الشامل ويتم استبعاد المرضى الذين يعانون من أعراض فشل عضلة القلب قبل بداية العلاج ،الذين يعانون من أمراض وراثية أو مكتسبة فى القلب، خلل فى وظائف الكبد أو الكلى أو عدم استقرار الحالة العامة للمريض أثناء العلاج أو الذين تعرضوا للعلاج الإشعاعى على الصدر فى مرحلة العلاج ويتم التقييم باستخدام الوسائل الآتية:

- تصوير أنسجة القلب بأشعة دوبلر.
- تصويرعضلة القلب بالأشعة فوق الصوتية التقليدية.
- قياس مادة تروبونين تى فى مصل الدم.
- قياس مادة برو بى إن بى فى مصل الدم.