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RESEARCH ARTICLE

STUDY THE EFFECT OF CHEMOTHERAPY ON THE CARDIAC FUNCTION.

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Abstract

Advances in cancer therapy have resulted in significant improvement in long-term survival for many types of cancer but have also resulted in untoward side effects associated with treatment. One such complication that has become increasingly recognized is the development of cardiomyopathy and heart failure. The anthracyclines are arguably one of the most active groups of chemotherapy agents in oncology. Echocardiography has been employed to measure left ventricular ejection fraction as chemotherapy progresses, and once decreases in function are identified, chemotherapy dosage or frequency is modified, or the chemotherapy is stopped**.**

Purpose: To detect the side effects of the chemotherapeutic agents on the cardiac function and to estimate the incidence and the features of subclinical cardiotoxicity induced after conventional treatment with doxorubicin-based chemotherapy for lymphoma and breast cancer patients

Patients and Methods: This observational non controlled cross sectional study conducted in order to identify the clinical and Echo-Doppler signs of cardiovascular affection induced by Anthracyclines–based chemotherapy in female patients with breast cancer and lymphoma.

Echocardiograms were performed before and 6 cycles after intiation of therapy with anthracyclines,. Clinical cardiomyopathy was defined by the presence of clinical signs of congestive heart failure (CHF) and decrease of left ventricular ejection fraction (EF). Cumulative dose of doxorubicin, diabetes, dyslipidemia, older age were evaluated as potential risk factors for the development of cardiac dysfunction.

Results: Cardiotoxic side effects developed in about one fourth of cancer breast patients and also lymphoma patients after Doxorubicin therapy .These toxicity were in the form of dilated cardiomyopathy (8.7%) in breast cancer patients and (8%) in lymphoma patients , pulmonary hypertension (7.3%) in breast cancer patients and (4%) in lymphoma patients, diastolic dysfunction (10%) in breast cancer patients and (12%) in lymphoma ,mitral regurgitation (12%)in breast cancer patients and (8%) in lymphoma patients and abnormal ECG changes (13 %).

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The most evident risk factors for the development of cardiotoxicity is the cumulative dose, advanced age, Diabetes Mellitus, Dyslipidemia and hypertension.anthracycline induced cardiomyopthy is related to number of received cycles of doxurubicin .A change in the left ventricular dimensions and functions (systolic and diastolic) as determined by echocardiography, may be an indicator of developing cardiotoxicity

Conclusion: chemotherapy induced cardiomyopathy is a serious complication of cancer therapy rendering the timely identification of high-risk patients the key to reducing this risk. A unified acceptable definition of chemotherapy induced cardiomyopathy adopted by cardiologists and oncologists must be developed.

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Introduction:-

Advances in cancer therapy have resulted in significant improvement in long-term survival for many types of cancer but have also resulted in untoward side effects associated with treatment. One such complication that has become increasingly recognized is the development of cardiomyopathy and heart failure. Whether a previously healthy person from a cardiovascular perspective develops cancer therapy–related cardiac dysfunction or a high-risk cardiovascular patient requires cancer therapy, the team of oncologists and cardiologists must be better equipped with an evidence-based approach to care for these patients across the spectrum. Although the toxicities associated with various cancer therapies are well recognized, limitations to our understanding of the appropriate course of action remain. ***(bloom et al , 2016)***

The anthracyclines are arguably one of the most active groups of chemotherapy agents in oncology. Commonly used anthracycline antibiotics include doxorubicin, daunorubicin, and epirubicin. They have proven activity against a spectrum of malignancies, including lymphoma,

gastric cancer, small cell lung cancer, sarcomas, and breast cancer to name a few. ***(von hoff et al , 1982)***

Anthracycline are not only some of the most effective, but also the most toxic, chemotherapeutic agents. Their use is associated with a dose-dependent, progressive, dilated cardiomyopathy. To date, there is no specific laboratory or imaging approach to proactively identify patients who will develop anthracycline-induced cardiotoxicity

Echocardiography has been employed to measure left ventricular ejection fraction as chemotherapy progresses, and once decreases in function are identified, chemotherapy dosage or frequency is modified, or the chemotherapy is stopped ***(Steinherz et al ,1991)***

Study design:-
prospective ,observational cross sectional study

Aim of the study:-
To identify the clinical and Echo-Doppler evidences of cardiovascular toxicity induced by Anthracyclines –based chemotherapy

Patients and Methods:-

This observational non controlled cross sectional study conducted in order to identify the clinical and Echo-Doppler signs of cardiovascular affection induced by Anthracyclines–based chemotherapy in female patients with breast cancer and lymphoma

Patients were selected from those attending National cancer institute and other specialized hospitals during the period from July 2014 to august 2016.

Inlusion criteria:-
150 women in different age groups who had breast cancer and 50 patients who had lymphoma . All received Doxorubicin –based chemotherapy,
according to the following regimen:
most of breast cancer patients had received **FEC** (fluorouracil 500 mg / m 2 , epirubicin 100 mg /m 2 and cyclophosphamide 500 mg /m 2) , and FEC -T regimen and lymphoma patients had received CHOP (cyclophosphamide 750 m g /m2 , doxorubicin 50-100mg /m2 , vincristin 1.4 mg/m2 , prednisone) according to type of lymphoma

Their baseline clinical and echocardiographic studies were essentially normal.

Exclusion criteria:-
Cardiac diseases: Ischemic heart disease, valvular,congenital heart disease or cardiomyopathy before initiation of chemotherapy.

Methods:-
All patients included in the study were subjected to the following:-
1. Full history taking: with special interest to determine the risk factors for CAD as hypertension, diabetes mellitus, smoking, dyslipedemia and positive family history of ischemic heart disease.
2. General clinical examination including pulse and blood pressure measurement.
3. Local cardiac examination for assessment of the presence of cardiac murmur, any additional heart sound (e.g. 3rd or 4th heart sound).
4. Echo-Doppler examination using General Electric system Vivid-5 machine with S3 probe. It was done to all patients before starting chemotherapy. The echocardiogram was performed with the patient breathing quietly and lying in the left lateral position. M mode , 2-D and Doppler examinations were done .

Echo-Doppler evaluation included:-
Transthoracic conventional echo Doppler was done in all standard views at all accessible windows.
* 2-D guided M- Mode at the level of the mid left ventricle was obtained and the following measurement was made according to the guideline of the American Society of Echocardiography ***(Cheitlin et al., 2003).***
(1) Interventricular septum thickness (IVST), left ventricular posterior wall thickness (LVPWT), end diastolic dimension (EDD), end systolic dimension (ESD), aortic root diameter (AO), and left atrial diameter (LA), Left ventricular function assessment by calculating percent fractional shortening (%FS) and ejection fraction (EF) as follows :
Fractional shortening (FS) was calculated using M-mode LV dimensions in diastole (LVDD) and systole (LVSD):
FS (%) = 100 X (LVDD – LVSD)/LVDD ***(Cheitlin et al., 2003).***
Ejection fractions% was calculated according to the following:
Systolic and diastolic volumes were calculated using the area–length method if the LV is symmetric, but the biplane modified Simpson's rule (4- and 2-chamber views) was used if there is a wall motion abnormality. The ejection fraction (EF%) was calculated according to the following equation:
EF (%) = 100 X diastolic volume – systolic volume/ diastolic volume ***(Cheitlin et al., 2003).***

(2) Wall motion abnormalities (hypokinesia , akinesia , dyskinesia and aneurysm) were searched.

(3) Evaluation of valvular structure and function especially the presence of mitral regurgitation ***(Weyman et al., 2007).***

(4) Evidence of pulmonary hypertension (PASP>30) as estimated through measurement of the tricuspid regurgitant peak velocity (Vmax). If the signal varies, we consider the highest value In absence of pulmonary stenosis and organic tricuspid regurgitation, the pulmonary artery systolic pressure is equal to: (V max) 2 X 4 + right atrial pressure. The right atrial pressure (RAP) was estimated from the diameter and effect of inspiration on the diameter of inferior vena cava as follows:
- Normal diameter (< 2 cm) with collapse or decrease > 50 %, the RAP = 5 mmHg.
- Normal diameter (2 cm) with decrease < 50%, the RAP = 10mmHg .
- Dilated (> 2cm) with decrease <50% , the RAP =15 mmHg .
- Dilated with dilated hepatic veins + no change, the RAP =20 mmHg. ***(Kircher et al.,1990).***

(5) Doppler assessment of LV diastolic function.

Indices of LV diastolic function obtained from standard transmitral diastolic Doppler signals.

These indices were derived from pulsed Doppler examination guided by color flow with the sample volume placed between the level of the mitral annulus and the tip of the opened mitral leaflets in the apical four chamber view. Measured and calculated Doppler parameters of diastolic function included: early diastolic velocity (E velocity), E-deceleration time,late diastolic velocity (A velocity) and ratio of early to late velocities (E/A) ***(Nagueh et al., 2009).***

Diastolic function was categorized according to the following:

- Normal diastolic function: when the E/ A ratio ≥ 1 and E – deceleration time < 250 msc.
- Grade I diastolic dysfunction (abnormal relaxation) when the E / A ratio < 1 and E – deceleration time > 250 msc .
- Grade II diastolic dysfunction (pseudo – normal) when the E / A ratio 1-2 and deceleration time between 150 – 200 msc .
- Grade III diastolic dysfunction (Restrictive Pattern) when the E / A ≥ 2 and the deceleration time < 150 msc. ***(Thomas et al.,2006)***

Follow-up:

Patients were followed up for 6 cycles with a monthly visit for clinical assessment of the symptoms and signs of cardiac affection.

Statistical methods:-

Data was analyzed using IBM SPSS advanced statistics version 22 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables. For not normally distributed quantitative data, comparison between two groups was done using Mann-Whitney test (non parametric t-test). Analysis of variance (ANOVA) with repeated measures was used to compare three consecutive measures of numerical variables. While for qualitative data comparison between more than two consecutive measures was done using Cochran test. All tests were two-tailed. A p-value < 0.05 was considered significant. ***(Bacchieri, Della. 2007).***

Results:-

This is observational non controlled cross sectional study included 200 patients admitted to National cancer institute and other specialized hospitals for receiving chemotherapy most of patients had breast carcinoma (150 patients) and the others had lymphoma (50 patients).

The age ranged between 30 to 60 years with a mean age of 43 ± 8.2 years. fourty six patients (23%) were hypertensives , fourty patients (20%) had Diabetes Mellitus, eleven patients (5%) had dyslipidemia and twelve patients (6%) had +ve family history cardiac problem

The results of the current study regarding clinical examination before and after chemotherapy showed that the mean HR before chemotherapy was 75 and after 77 , systolic blood pressure before was 121 and after 123 and diastolic blood pressure before was 70 and after 78 as in

Table (7) showed that there is no significant difference between the different echocardiographic parameters before and 6 months after chemotherapy except for the incidence of mitral regurgitation in 18 (12%)in patients with breast cancer and 4 (8%) in lymphoma patients , the incidence of diastolic dysfunction which occurred in 15 (10%)in breast cancer patients and 6 (12%) in lymphoma patients , incidence of increased LV dimensions in 13 (8.7%) in breast cancer patients and 4 (8 %) in lymphoma patients ,, incidence of decline in EF is 10(6.7%) in breast cancer patients and 4(8 %) in lymphoma patients incidence of pulmonary HTN in 11(7.3 %)in breast cancer patients and 2(4 %)in lymphoma patients.

Table (7):- Results of echocardiographic study before and 6 months after chemotherapy

Type of Complication	Complication Rate in BREAST CANCER PATIENTS No (%)	Complication Rate in In LYMPHOMA PATIENTS No (%)	COMPLICATION RATE IN ALL CASES
Dilated Cardiomyopathy	13 (8.7%)	4 (8%)	17 (8.5 %
Pulmonary hypertension	11 (7.3%)	2 (4%)	13(6.5%)
Mitral regurgitation	18 (12%)	4 (8%)	22 (11 %)
Diastolic Dysfunction	15 (10%)	6 (12%)	21 (10.5 %)
Low EF	10 (6.7 %)	4 (8%)	14 (7%)

Table (8):- Incidence of Cardiac Complications after chemotherapy

	Before N = 200	After N = 200	P value
EDD (Mean ± SD) (Cm)	4.2 ± 0.3	4.4 ± 0.6	> 0.05
ESD (Mean ± SD) (Cm)	2.9 ± 0.5	3.0 ± 0.6	> 0.05
PWT (Mean ± SD) (Cm)	0. 8 ± 0.1	0.9 ± 0.1	> 0.05
SWT (Mean ± SD) (Cm)	0.77 ± 0.1	0.82 ± 0.1	> 0.05
RVDD (Mean ± SD) (Cm)	1.3 ± 0.4	1.34 ± 0.3	> 0.05
LAD (Mean ± SD) (Cm)	3.3 ± 0.5	3.4 ± 0.4	> 0.05
Ao. (Mean ± SD) (Cm)	3.1 ± 0.35	3.3 ± 0.4	> 0.05
EF% (Mean ± SD) (Cm)	64.6% ± 5	63.3 ± 5.9	< 0.05
FS% (Mean ± SD) (Cm)	37.8 ± 7.1	36.0 ± 6.8	< 0.05
Mitral Regurgitation (n (%)*	0	22 (11%)	< 0.05
Diastolic dysfunction (n (%)**	0	21(10.5%)	< 0.05
Pulmonary hypertesion(n %)		13(6.5 %)	< 0.05

the current study showed that dilated cardiomyopathy developed in 17 patients (8.5%), pulmonary hypertension occurred in 13 patients (6.5%), significant mitral regurgitation in 2 2 patients (11%), diastolic dysfunction in 21 patients (10.5 %),and low EF in 14 patients (7 %) The total number of patients who developed one or more cardiac complication was 52 (26%) i . e . about one fourth of cases .

Discussion:-

Anthracyclines are among the most widely used chemotherapeutic agents ,and have been shown to be effective in awide range of tumers in particlar breast cancer and lymphoma.their clinical effectivness however may be thwarted by the development of cardiotoxicity that negatively affects patients outcomes,and seriously limits their oncologic therapeutic opportunities (**Smith etal.,2010 and Vandalen et al .,2007)**

Chemotherapy induced cardiotoxicity in cancer patients may causes serious consequences not only in patients with existing cardiovascular disease but also in patients with good prognosis , this cardiotoxicity may eventually cause severe morbidityleading to premature death (**Svoboda et al .,2012)**

The most clinical presentation of cardiotoxicity is dose dependent cardiomyopathy leading to chronic heart failure , frequently occurring after administration of chemotherapy including anthracyclines (**Yeh et al., 2004)**

Such cardiotoxicity results in a permanent loss of cardiac myocytes and a progressive reduction in cardiac function. Initially, damage to the heart is subclinical; however, increasingly impaired cardiac function can result in clinical heart disease, with serious cardiac injury resulting in congestive heart failure.**(Kilickap et al., 2005)**

Early detection of subclinical anthracycline cardiotoxicity , and ultimately the prevention of clinical congestive heart failure ,is a continuing challenge in clinical practice.

This prospective clinical trial aimed at identifying the clinical and echocardiographic signs of cardiovascular toxicity induced by anthracycline containing regimens among patients with breast cancer and lymphoma . For this purpose, one hundred women with breast cancer who underwent mastectomy and fifty patients with Hodgkin and non Hodgkin subjected to FEC (fluorouracil, epirubicin and cyclophosphamide) , CHOP (cyclophosphamide, doxorubicin, vincristin, prednisone) and respectively (anthracycline containing regimens) were used in this study . Their baseline clinical and echocardiographic examinations (before starting chemotherapy) were essentially normal .They were followed-up clinically for 6 months with repeated echocardiographic study done at the end of the follow - up period

The mean age in our study was 43 ± 8.2 years ranged from 30-60 years this was concordant with **Jensen et al ., 2002** who reported that the incidence of congestive heart failure is greater with old patients compared with younger age and disconcordant with **Peinf et al ., 2004** who reported that the incidence of anthracycline induced cardiomyopathy increases with young age

In our study diabetes is important risk factor associated with chemotherapy ,it is present in 20 % of patients ,this was concordant with **lioyd et al ., 2006** ,, and disconcordant with **danesi et al ., 1999**

In our study , diastolic blood pressure increased significantly, that was concordant with **Shakir et al ., 2009** , and disconcordant with **Mellstedt et al .,2003**

In our study the incidence of symptomatic heart failure is 7 % , this was concordant with **Keefe et al., 2001** and also von hoff et al **.,**1979 , and disconcordant with **Borrow et al., 1983**

The results of the current study regarding clinical examination before and after chemotherapy showed that Dyspnoea and murmur of mitral regurgitation developed in 14 (7%) and 22 (11%) cases respectively after chemotherapy this was concordant with **Shakir et al., 2009** who reported that an incidence of clinical heart failure and cardiomyopathy was 5 to 20 % which is nearly similar to that recorded in our study.

In the current study The incidence of abnormal findings in the ECG developed in 26 patients (13%). Consistent with these results, **Dresdal et al., 1983** who reported that the incidence of ECG changes was 12-14%.

Additionally , **Frishman et al., 1997**concluded that the ECG abnormalities due to anthracycline therapy may present as non – specific ST and T wave changes, T wave flattening , decreased QRS voltage and prolongation of Q-T interval. They added that sinus tachycardia is the most common rhythm disturbance. they reported that the incidence of the ECG changes in their study was 20-30%- compared to only 14% in the present study.

The results of the present study regarding the echocardiographic findings before and after chemotherapy showed that there is no significant increase in cardiac chambers cavity dimensions and significant decrease in the LV systolic function (EF % and FS %).

twenty two patients (11 %) developed mild to moderate mitral regurgitation while twenty one patients (10.5%) developed diastolic dysfunction this was concordant with **Kruipicke et al ., 2002** who did not show significant changes of M-mode derived LV end diastolic and end systolic dimensions ,, also was concordant with **Gabrielsen et al ., 2002** who reported that there was significant decline in mean ejection fraction after chemotherapy , the mean diastolic left ventricular dimension did not significantly change

This was disconcordant with **Singal et al ., 1998** who reported that end systolic dimension increased significantly after completion of chemotherapy

In our study the incidence of chemotherapy induced cardiomyopathy was 8.7% in breast cancer patients with cumulative dose of doxorubicin 600-800mg/m^2 and 8% in lymphoma patients with cumulative dose 400-600mg /m^2. this was concordant with **Salvaterelli et al., 2015** and **Von Hoff et al .,1979**., it was disconcordant with **Swain et al., 1997** who reported that the incidence of chemotherapy induced cardiomyopathy at dose of 550 mg /m^2 was 26%

Conclusions and Recommendations:-

- Cardiotoxic side effects developed in about one fourth of cancer breast patients and also lymphoma patients after Doxorubicin therapy .These toxicity were in the form of dilated cardiomyopathy (8.7%) in breast cancer patients and (8%) in lymphoma patients , pulmonary hypertension (7.3%) in breast cancer patients and (4%) in lymphoma patients, diastolic dysfunction (10%) in breast cancer patients and (12%) in lymphoma ,mitral regurgitation (12%)in breast cancer patients and (8%) in lymphoma patients and abnormal ECG changes (13 %).
- The most evident risk factors for the development of cardiotoxicity is the cumulative dose, advanced age, Diabetes Mellitus, Dyslipidemia and hypertension.
- anthracycline induced cardiomyopthy is related to number of received cycles of doxorubicin.
- anthrcycline analogues have shown some benefit in reducing cardiotoxicity when compared with doxorubicin alone.
- A change in the left ventricular dimensions and functions (systolic and diastolic) as determined by echocardiography, may be an indicator of developing cardiotoxicity; So, monitoring such changes should be frequent during treatment and regular thereafter, throughout the patient's lifetime.
- It is recommended that other studies should be done on a larger scale and for a longer follow up period to shed more light on this important issue.

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