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Use of left ventricle longitudinal function parameters for detection of subclinical impairment of LV systolic function in patients with hematological malignancy on cardiotoxic chemotherapy

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Abstract

Background:-
Cardiac toxicity remains an important side effect of anticancer therapies, leading to increased morbidity and mortality due to mainly heart failure, myocardial ischemia, arrhythmias, hypertension and thromboembolism which can negatively affect the quality of life as well as the prognosis of oncologic patients (1).

Objective:-
1-Detection of subclinical left ventricular systolic dysfunction in patients with hematological malignancy treated with chemotherapy with normal ejection fraction.
2- compare sensitivity and specificity between different LV longitrudinal function parameters for hematological malignancy patient on chemotherapy.

Patients and Methods:-
A case – control cross sectional study conducted at Baghdad teaching hospital, cardiology department (Echocardiographic lab.) during period from May 2018 to May 2019. Eighty-five patients with different types of hematological malignancies on chemotherapy and seventy-eight patients with different types of hematological malignancies not taking chemotherapy (as controls) were enrolled.
Patients were excluded if they had one of the conditions that could affect the heart functions, had impaired left ventricular EF or those with bad echocardiographic image quality. Data were collected by using a pre-constructed data collection form (questionnaire). Data were analyzed by using the statistical package for social sciences (SPSS) version 24.
All studied patients were subjected to comprehensive echocardiographic examination, including two dimensional, M-mode, Doppler and tissue Doppler and two dimension speckle tracking imaging, in addition to routine echocardiographic measurements, mitral annular plane systolic excursion , tissue Doppler systolic velocity and global longitudinal strain (S and GLS) where measured in all patients .

Results:-
The studied patients aged 17-65 years, of both genders. All of the patients taking doxorubicin with mean cumulative dose 201±140 and other chemotherapeutic agents was taken in different percent's
The mean ejection fraction (EF) was lower in cases than controls (P<0.05) in spite of normal values of EF in both cases and control .
Patients who were taking chemotherapy had a significant abnormality in the MAPSE, LV mean S `and GLS with equal segment involvement. (P-value< 0.05).
Also by comparing the three echocardiography parameters taken in study, the MAPSE sensitivity and specificity were 82% and 93% respectively, and S` sensitivity and specificity were 89% and 95% respectively, and GLS sensitivity and specificity were 94% and 97.5% respectively.
Conclusions:
Myocardial strain imaging, is the most sensitive and specific echocardiography parameter for detection of subclinical LV systolic dysfunction of patients on chemotherapy and MAPSE and S` are more sensitive and specific than EF.
The use of these parameters are expected to detect left ventricle dysfunction at an earlier stage with possible early intervention to prevent progression and improve outcome.

Keywords: Cardiac toxicity, hematological malignancy, echocardiographic examination, MAPSE.

Introduction

A significant proportion of cancer survivor are living with long term adverse effect of cancer therapy, involving multiple organ systems. Cardiovascular toxicity of cancer therapy is the major concern of in this regard. (1).

Historically, several definitions of cardiotoxicity have been proposed. The most commonly used definition is a 5% reduction in symptomatic patients (or 10% reduction in asymptomatic patients) in the left ventricular ejection fraction (LVEF) from baseline to an LVEF <55% (2)The use of LVEF has important limitations. **First**, the measurement of LVEF is subject to technique-related variability, which can be higher than the thresholds used to define cardiotoxicity **Second,** the reduction in LVEF is often a late phenomenon, with failure to recover systolic function in up to 58% of patients despite intervention (3).

Current anticancer therapies are associated with unique and various degrees of direct (e.g., myocardial toxicity, ischemia, hypertension, arrhythmias) as well as indirect cardiovascular insults (e.g., unfavorable lifestyle changes). Cardiovascular diseases are not always caused by toxicity from cancer therapy exposures, and they can be normal disease processes in older adults. The incidence of cancer treatment-induced cardiovascular injury varies and widely, depending on the specific cancer therapy used, duration of therapy, and underlying patient comorbidities. (4).

Cardiotoxic chemotherapy: -

Anthracycline:-

Anthracycline are among the most widely utilized antineoplastic agents and include doxorubicin, liposomal doxorubicin, daunorubicin, idarubicin, and epirubicin. These agents are frequently used in curative and palliative regimens for breast cancer, lymphomas, sarcomas, acute leukemia, and other cancers. Anthracycline-induced cardiotoxicity was first reported as early as 1967 in children receiving doxorubicin. (4)

Systolic dysfunction occurs by a number of mechanisms including increase in myocardial interstitial pressure causing a decreases in coronary blood flow culminating.to cardiac ischemia. In addition to the aforementioned, conversion of anthracyclines to secondary alcohol metabolites in cardiac myocytes lead to poorclearance and greater accumulation in the heart. This in turn contributes to cardiotoxicity both during and for a protracted period of time after completion of chemotherapy. A new interesting pre-clinical study showed that cardiomyocytes-specific deletion of Top2b (encoding topoisomerase-IIß) protects cardiomyocytes from doxorubicin induced DNA double-strand breaks and transcription changes which cause defective mitochondrial biogenesis. In the preclinical study the aforementioned deletion protected mice from the development of doxorubicin-induced heart failure suggesting that cardiotoxicity is mediated by topoisomerase-IIß in cardiomyocytes. (5,6)

Anthracycline cardiotoxicity is categorized as acute and chronic. Acute cardiotoxicity occurs during or soon after initiation of therapy. This is usually transient and self-limiting with a myopericarditis like picture, non-specific repolarization changes on ECG, dysrhythmias, troponin elevation, and transient LV dysfunction. These abnormalities usually resolve spontaneously with only supportive therapy. In contrast, chronic cardiotoxicity is the most common and relevant form of Anthracycline cardiotoxicity. This comprises of LV systolic dysfunction, which is insidious in onset and asymptomatic in the early stages, but can progress to dilated cardiomyopathy and overt CHF, which is generally irreversible. (7)

Chronic cardiotoxicity is arbitrarily classified as type 1 or early onset (typically detected within one year of completion of chemotherapy) and type 2 or late-onset (usually detected after the first year with an unlimited time frame of up to decades after completion of chemotherapy). Majority of the patients develop chronic cardiotoxicity within the first year of completing therapy. (8,9).

Asymptomatic and subclinical LV dysfunction generally precedes overt CHF. A prompt discontinuation of anthracycline therapy with the onset of asymptomatic LV dysfunction can prevent its progression to CHF and is pivotal to the current strategies for the prevention of anthracycline related CHF. Chronic Anthracycline cardiotoxicity can also present as restrictive cardiomyopathy with diastolic dysfunction and heart failure with concomitant mediastinal irradiation. Prior to the widespread use of serial LV function monitoring, the incidence of CHF with doxorubicin was 4–7% in patients receiving 400 to 550 mg/m2, 18% in those receiving 551 to 700 mg/m2, and 30% at doses above 701 mg/m2 (10).

Many potential risk factors have been identified for anthracycline-induced cardiotoxicity as lifetime cumulative dose,intravenous bolus administration, high single doses, history of cardiovascular disease, diabetes mellitus (DM), andexcessive alcohol intake, longer time since therapy completion, and increased cardiac biomarkers (e.g., troponins and natriuretic peptides) during and after treatment (11).

An approach of serial LV function monitoring during anthracycline therapy and discontinuing further therapy at the appearance of subclinical LV dysfunction remains the most effective strategy for preventing overt CHF were developed based on the analysis of these studies (table-1.1). (12)

Table 1.1 Recommendations for monitoring LVEF during doxorubicin therapy

EF	Dose of anthracycline	Cardiotoxicity
Normal (EF≥50%)	Prior to starting chemotherapy At 250-300 mg/m2 At 400-450 mg/m2 Prior each subsequent cycle	≥ 10% EF fall to EF ≤ 50%
30-50 % < 30%	Prior starting therapy Prior each subsequent dose Avoid doxorubicin	≥ 10% EF fall

Cyclophosphamide

Cyclophosphamide, an alkylating agent, has been reported to cause left ventricular dysfunction in 7-28% of patients and case reports of treatment-related pericardial effusions and pericarditis have also been published. The exact mechanism of cardiotoxicity is unknown, but it has been hypothesized that cyclophosphamide causes direct endothelial injury followed by extravasation of toxic metabolites (13).

5-flourouracile and other antimetabolites: -

Cardiotoxicity has been reported in up to 2–4% of patients receiving the antimetabolite 5-fluorouracil or its analogues. 5-flurouracil can cause coronary vasospasm resulting in chestpain, myocardial ischemia, myocardial infarction, and death. (7)

Vinca Alkaloids

The vinca alkaloids were the first class of microtubule-targeting drugs to be utilized to abrogate cancer, vinca alkaloids as vincristine and vinblastine are commonly used in the treatment of leukemia and lymphoma among other malignancies, Cardiotoxicity with vinca alkaloids includes myocardial infarction, hypertension, angina, and vaso-occlusive complications. In addition, this class of drugs can also cause Prinzmetal angina which suggests coronary spasms as the culprit behind cardiac ischemia as opposed to coronary structural blockade or arrhythmia.(8)

Arsenic Trioxide

Arsenic trioxide is a cytotoxic agent commonly used in the treatment of acutepromyelocytic leukemia. One of the most common adverse cardiovascular events is QTc prolongation, occurring in 26-93% of patients; the incidence of torsado de pointes (TdP) can be as high as 15%. The mechanism of arsenic trioxide in QTc prolongation is unclear; one hypothesis proposed could be the neuropathy of cardiac sympathetic system as arsenic trioxide is known to affect the peripheral nervous system and cause sympathetic input imbalance.(9)

Echocardiography

Imaging techniques are conventionally applied in monitoring of chemotherapy-related cardiotoxicity to determine left ventricular ejection fraction, echocardiography has become the dominant cardiac imaging technique due to its portability and versatility. Two-dimensional (2D) echocardiography is currently the first line imaging modality for assessing global and regional function.(14)

A-left ventricle ejection fraction (EF):-

LVEF is the most commonly accepted parameter of cardiac function that independently predicts short-term and long term mortality from CV events, including myocardial infarction, ischemic and idiopathic cardiomyopathy, as well as anthracycline-induced cardiomyopathy. However, the measurement of LVEF presents several challenges related to image quality, assumption of LV geometry, load dependency, and expertise. Moreover, LVEF measurement remains a relatively insensitive tool for detecting cardiotoxicity at an early stage. This is largely because a decrease in LVEF does not occur until a critical amount of myocardial damage has taken place and cardiac compensatory mechanisms are exhausted (15).

LV Ejection Fraction by M-Mode:-

The American Society of Echocardiography (ASE) recommends measurement of LV dimensions with the M-mode line perpendicular to the long axis of the heart and immediately distal to the tips of the mitral valve leaflets in the parasternal long axis view(15)
Ejection Fraction= [(EDV – ESV)/EDV] *100(15)
Normal Values of Ejection Fraction(15)

- Male EF=52-72%
- Female EF=54-74%

Simpsons method (biplane method):-

This method has been shown to be the most accurate. This method involves manual tracing of the LV cavity endocardium at end-systole and end-diastole, from the apical 4-chamber view and the apical 2 chamber view, The machine's software then divides the cavities into many parallel discs, calculate the volume of each disc and automatically combines the volume to provide the user with estimated LV cavity volume in end diastole (LVEDV) and end systole (LVESV). Simpson's rule assumes the LV cavity to be ellipsoidal at all times (15,16).

B-Mitral Annular Plane Systolic Excursion (MAPSE)

M-mode measurement that has been employed is the descent of the base. During ventricular contraction, the base (annulus) of the heart moves toward the apex. In the presence of global left ventricular dysfunction, the magnitude of this motion is directly proportional to systolic function. M-mode interrogation is undertaken of the lateral mitral annulus, and annular excursion toward the transducer is then calculated There is a relatively linear correlation between the magnitude of systolic annular excursion and global systolic function. (16)

Normal values(17) : -

Men > 13 mm
Women > 11 mm

C- Tissue Doppler Imaging (Mitral Annular Peak Systolic Velocity):-

A sample volume can be placed within the mitral annulus or myocardium and quantitative information extracted regarding tissue velocity Annular systolic velocity(s`) is a marker of global left ventricular function in a uniformly contracting ventricle. Normal values Tissue Doppler Imaging Doppler tissue peak systolic velocity(S`) (cm/s). normally ≥ 9 cm/sec (16,17)

D-Myocardial strain:-

Newer technology has emerged that allows for an improvement in the accuracy of calculating LV function. One of the most promising is strain-echocardiography. Strain is a measurement of myocardial deformation. As the ventricle contracts muscle shortens in the longitudinal and circumferential dimensions and thickens and lengthens in the radial direction. Strain imaging can provide an assessment of global and regional cardiac function and can be measured using either tissue Doppler or 2D-based methods. (18)

Strain & Strain Rate:- Strain is represented as change in length normalized to original length while strain rate is at which time this change occurs(16)

LV Longitudinal Strain:-

It can be acquired in apical long axis view, apical 2 chambers and apical 4 chambers.(17)

Normal Values of Longitudinal Strain:-

Normal values for GLS depend on the definition of the measurement position in the myocardium, the vendor, and the version of the analysis software, result in inconsiderable heterogeneity. To provide some guidance, a peak GLS in the range of -19% can be expected in a healthy person. (17)

There is evidence that women have slightly higher absolute values of GLS than men and that strain values decrease with age. (19)

Aims of the study:-

1-Early detection of left ventricular systolic dysfunction for hematological malignancy patient treated with chemotherapy with normal ejection fraction depending on mitral annular plane systolic excursion (MAPSE), tissue Doppler systolic velocity (S`) and global longitudinal strain (GLS).

2- comparison of sensitivity and specificity of echocardiography parameters (MAPSE, S`, and GLS) in detection of LV systolic dysfunction for hematological malignancy patients on chemotherapy.

Patients and Methods

Study's design: -

A case control study cross sectional study, conducted in Baghdad teaching hospital, cardiology department, echocardiography laboratory. The study was conducted during the period 1st of May 2018 to 1st May 2019.

The echo study was done by one examiner (researcher), using the echocardiography device (Philips CX50), that has TDI capabilities and phased array transducer frequency of 2.5 MHz examination was undertaken in the left lateral decubitus position.
Cumulative doses was calculating depending on follow-up copybook which contain the detailed chemotherapy schedule and doses.

Inclusion criteria:-

Patients were referred to the echocardiography laboratory from the hematology department for LV function assessment before or during chemotherapy.
Patients

included have: -**1-** Normal function in the phase of chemotherapy that was defined by stability of Ejection Fraction ≥54% in female and ≥ 52% in male, measured by Simpson method.**2-** Good images high frame rate 2D acquisitions for speckle strain analysis.

Exclusion criteria: -

Any patient with any of the following condition was excluded from the study: -**1-** hypertension**. 2-** DM**. 3-** ischemic heart disease**. 4-** cardiomyopathy

5- radiation therapy of the chest **6-** cardiac arrthymia. **7-** valvular heart disease.**8-** rheumatic heart disease**. 9-** chronic alcohol drinking**. 10-** drug (e.g. b- blockers or ca-channel blockers).**11-** any patient with impaired EF (< 54% in female and <52% in male).

Method and Echocardiography: -

Echocardiographic examination and measurements are done according to recommendations of American society of echocardiography.

LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and ejection fraction (EF) were measured using Simpson`s method. Ejection Fraction was considered abnormal if EF<54% in female and < 52% in male.

Mitral annular plane systolic excursion (MAPSE) was measured using M-mode imaging in the apical four chamber view. The M-mode cursor was placed on the lateral mitral annulus as much parallel as possible to the LV walls. MAPSE < 13 mm in male or < 11 in female was considered abnormal.

Pulsed wave tissue Doppler echocardiography (TDE) was used to measure, mitral annular peak systolic velocity (S′) at the lateral and septal site of the mitral annulus. and if the average of both, is < 9 cm/s it was considered abnormal.

Global longitudinal strain (GLS) was measured using speckle tracking echocardiography. Apical 3, 2, and 4 chambers high frame rate grayscale acquisitions (40 to 80 frames/s) were obtained with commercially available equipment Philips CX-50. GLS was measured for 3, 2, and 4 chamber views separately Segmental strain was presented as a bull- eye map and GLS was automatically. Calculated The strain cutoff -19 was used as a lower normal value, any reading below -19 considered abnormal.

All measurements were taken along with simultaneous electrocardiogram at a speed of 25 mm/s during three consecutive heart cycles, and the mean values were calculated.

Statistical analysis:-

Data of all cases and controls were entered, managed and analyzed by using the statistical package for social sciences (SPSS) version 24, IBM, US, 2014. Descriptive statistics were presented as frequencies (number) and percent (%), for categorical variables (gender, diagnosis, types of cytotoxic drugs,), and as a mean with standard deviation (SD) for continuous variables (age in years, cumulative dose of chemotherapies, EF, systolic tissue Doppler parameter (S`), MAPSE, and GLS).

Chi square test was used to assess the significance of the differences in frequencies of categorical variables, and also used to detect the sensitivity and specificity for each parameter.

Study t-test was used to assess the significance of differences in mean values of the continuous variables. A P-value < 0.05 was considered statistically significant.

Results

A total of 85 patients (43 males and 42 female) and with different hematological malignancies on chemotherapy(as cases), in addition to 78 patients (40 males and 38 female) with different hematological malignancy without chemotherapy (as a controls) were enrolled in this study, comparing the sample size of cases and control shows no significant difference with (P-value= 0.129), also by comparing both male and female number for cases and control shows no significant differences with (P= 0.072 for male and P= 0.068 for females).

The mean age of patients on chemotherapy was 42.2 ±13.8year and for controls was 40.79± 15.2years with no statistically significant difference (P=0.18).

The mean weight of the cases was 73.5±10.5 Kg while the mean weight of the control was 77.3±11.5Kg without significant difference between them with (P=0.996).

The mean height of the cases was 165.8±9.11 cm and the mean height of the control was 166.9±7.21 cm without significant difference between them with (P=0.244).

The mean body surface area of the cases 1.84±0.167 m2, while the mean body surface area of the control was 1.88±0.171m2 without significant differences between them with (P= 0.940). see table (3.1)

Table (3.1) shows demographic criteria for the cases and controls

Characters		Cases (85)		Control (78)		P-value
No. of patients		85		78		P =0.129
Gender (%)	Male (%)	43	51.7%	40	48.7%	P= 0.072
	Female (%)	42	48.3%	38	51.3%	P=0.068
Age(years) (Mean ± SD)		42.2 ±13.8		40.79± 15.2		P=0.18
Weight(kg) (Mean±SD)		73.5±10.5		77.3±11.5		P=0.996
Height(cm) (Mean±SD)		165.8±9.11		166.9±7.21		P=0.244
Surface area(m2) (Mean± SD)		1.84±0.167		1.88±0.171		P=0.940

Table (3.2) summarizes the distribution of the cytotoxic drugs used in different combined regimens for the treatment of hematological malignancies among Patients, with it is cumulative dose. Doxorubicin (DOX) was the dominant medication used in all Patients85 (100%) followed by cytarabine (Ara-c) 50 (59%), cyclophosphamide 43 (51%), Vincristine 38 (45%), etoposide 26 (30%), methotrexate (MTX)17 (20%), vinblastine 6 (7%), cisplatinum 5(6%), and bleomycin 4 (5%)

Table (3.2) shows number of patients taking chemotherapy, with cumulative dose

Chemotherapy	Number of patients	Percent (%)	Cumulative dose (mg/m2) (Mean±SD)
Doxorubicin	85	100%	201± 140
Ara-c	50	59%	870±102
Cyclophosphamide	43	51%	2197±511
VCR	38	45%	7.6±2.7
Etoposide	26	30%	679±214
MTX	17	20%	90±25
Vinblastin	6	7%	72±15
Cisplatinum	5	6%	200±28.8
Bleomycin	4	5%	63±18.7

The mean ejection fraction (EF) of cases was (62.6± 6. 35%) and for control it was (67.3± 8.34 %) . Although both patients and control had EF within the normal ranges, the difference was statistically significant (P=0.024), patients had lower EF than controls. .

The mean MAPSE for the cases was 10.78± 3.435 while the mean MAPSE for the control group was 13.34± 2.253 with significant difference between both group (P= 0.0083).

The mean S` for the cases was 8.3±3.232 while the mean S` for the control group was 11.2±3.88 with significant difference between both groups with (P= 0.0076).

The mean GLS for the cases was -16.43±2.398 while the mean GLS for the control group was - 22.4±3.04 with significant difference between both groups (P= 0.0016)

The mean GLS in A3C view in cases was -19.22±1.87 while mean GLS in A3C view for the control group was -21.87±7.72 with significant difference between both groups with (P=0.00071). The mean GLS in A4C view in cases was -16.13±3.12while mean GLS in A4C view for the control group was -19.012±3.04with significant difference between both groups with (P=0.00104).The mean GLS in A2C view in cases was -16.43±1.93 while mean GLS in A2C view for the control group was -23.16± 4.12with significant difference between both groups with (P=0.00312).All echo data is shown in the table (3.3).

Table (3.3) Comparison between cases and controls in EF and longitudinal LV systolic function parameters

Parameters	Case (Mean± SD)	Control (Mean ±SD)	P-value
EF %	62.6± 6. 35	67.3± 8.34	P= 0.024
MAPSE(mm)	10.78± 3.435	13.34± 2.253	0.0083
S`(cm/sec)	7.3±3.232	11.2±3.88	0.0076
GLS (Mean)	-16.43±2.398	-22.4±3.04	0.0016
A3C	-18.22±1.87	-21.87±7.72	0.00071
A4C	-16.13±3.12	-20.012±3.04	0.00104
A2C	-16.43±1.93	-23.16± 4.12	0.00312

The table (3.4) shows that most of the cases has abnormal MAPSE is 70 (82%), and 15(18%) of cases with normal MAPSE, as compared with control, 5 (7%) of them with abnormal MAPSE and73 (93%) of control with normal MAPSE. From the table we conclude the sensitivity of MAPSE test is 82% and specificity is 93% in detection of LV systolic dysfunction.

The table (3.4) shows most of the cases has abnormal S`is76 (89%), and 9 (11%) of cases with normal S`, as compared with control, 4 (5%) of them with abnormal S` and 74 (94%) of control with normal S. From table we conclude the sensitivity of S` test is 89% and specificity is 94% in detection of LV systolic dysfunction.

The table (3.3) shows most of the cases has abnormal GLS 80(94%), and 5(6%) of cases with normal GLS, as compared with control, 2 (2.5%) of them with abnormal GLS and 76 (97.5%) of control with normal GLS..From table we conclude the sensitivity of GLS test is 94% and specificity is 97.5% in detection of LV systolic dysfunction.

Table (3.4) shows the numbers and the percent of cases and control with normal and abnormal longitudinal LV function parameters

	Cases (number / %)	Control (number/%)
Abnormal MAPSE	70 (82%)	5 (7%)
Normal MAPSE	15 (18%)	73 (93%)
	Sensitivity= 82%	Specificity= 93%
S`< 9 cm/sec	76 (89%)	4 (5%)
S`≥ 9 cm/sec	9 (11%)	74 (95%)
	Sensitivity= 89%	Specificity=95%
GLS < -19 cm/sec	80 (94%)	2 (2.5%)
GLS ≥ -19 cm/sec	5 (6%)	76 (97.5%)
	Sensitivity= 94%	Specificity= 97.5%

Discussion

Cardiac toxicity remains an important side effect of anticancer therapies, leading to increased morbidity and mortality due to mainly heart failure, myocardial ischemia, arrhythmias, hypertension and thromboembolism which can negatively affect the quality of life as well as the prognosis of oncologic patients(1)Therefore, contemporary management of patients with cancer should include careful consideration of potential cardiotoxicity during therapy, with a focus on early detection and intervention(2).

Male patients were equally distributed with females in the present study. This findings is consistent with **Dahi DM, in Baghdad (2014)**(20) and **Sysa-Shah P, et al study in USA (2014)**(21) but This finding is inconsistent with **Mohammed SK et al study in Iraq** (2014)(22) and **Weldetsadik AT** study in Ethiopia (2013) (23) .which reported predominance of male gender among hematological malignancies, This inconsistency might be attributed to small sample size of present study in comparison to previous literatures and, additionally, the differences in study design.

In the current study, the demographic picture of the studied group revealed a mean age of patients with hematological malignancies of 42±13.8 years. This finding is close to results of **Hossain MS, et al study in Bangladesh (2014)**(24) which shows mean age of cases is 41±10.45 year, .Also This finding is close to results of **Dahi DM, in Baghdad (2014)**(20) , that reported mean age of studied patients with hematological malignancies was of 39.7±14.2 years. On the other hand, this reported mean age of studied patients was much lower than the results of **Smith A, et al study in UK (2011)**(25) that revealed mean age of hematological malignancies patients in UK for period 2004-2009 of 70.6 years. It is generally argued that young age phenomenon of cancers might be due to the lower life expectancy and younger population structure of a developing country.

The main cytotoxic therapy studied in this thesis was Doxorubicin (100%). this finding is consistent with results of **Sysa-Shah P, et alstudy in USA (2014)**(21) **Dahi DM, in Baghdad (2014)**(20) that reported wide use of Doxorubicin in hematological cancers(100%), which is one of Anthracycline chemotherapy that considered an effective therapy for numerous types of malignancies.

The mean cumulative dose of the doxorubicin is 201± 140 mg, this is consistent with **Dahi DM, in Baghdad (2014)**(20) in which the mean cumulative dose of thedoxorubicin is 158±74.8 mg, also consistent with **(Stoodley et al., 2011)**(27) With mean cumulative dose is 219± 110 mg, this is safe dose usually given for avoidance of cardiotoxic effects of chemotherapy.
The current study reported that the mean ejection fraction percent was significantly lower among cases (p=0.024) as compared with control group. This finding is consistent with results of **Alihanoĝlu YI, et al study in Turkey (2012)**(28) that report (P-value= 0.0086) and **Shore T, et al study in USA (2001)**(29). Reporting (P-value=0.00341),and low ejection fraction of patients was significantly correlated with taking Doxorubicin and Cyclophosphamide that may cause reduction in EF as compared with patient not taking chemotherapy .

MAPSE is one of the parameters used to quantify long-axis LV systolic, function .In this study, results MAPSE has benefit in detection of subclinical LV systolic dysfunction of patients on chemotherapy, with (P value = 0,0083) . this study is the same result that mitral annular plane systolic excursion can be used as a sensitive tool to detect early longitudinal LV systolic dysfunction **Joanna Luszczak et al.,2013).**(30) that with report (P-value= 0.0062)

The tissue Doppler parameters show mainly significantly differences for patients compared to controls (P=0,0076). This finding is similar to results of **Mercuro G, et al** study in Italy (2007) (31) that shows (P-value= 0.021).

A relative reduction in GLS observed after taking chemotherapy as (P= 0.0016) with no specific segment involved rather than others (all segments involved uniformly) which provides confirmation of observations reported previous study **Stoodley et al., 2011**(27) and similar to another study that stated the ability of longitudinal systolic strain to detect sub-clinical changes in LV systolic function in patients receiving anthracycline chemotherapy **Yu Kang et al., 2013**(26)

Our study shows that the most sensitive and specific parameter to detect LV systolic dysfunction is the GLS with sensitivity 94% and specificity 97.5%, this data correlate with study **Stoodley et al., 2011**(27) and **Yu Kang etal.,2013**(26)That states that the most sensitive parameter for detection of subclinical systolic dysfunction of patient on chemotherapy is

GLS, followed by S` then MAPSE and all is more sensitive and specific than EF which is similar to our findings .

Limitations of the study:-

1. Small sample size.
2. The study design did not allow follow-up of cases during chemotherapy.
3. Subclinical or silent coronary artery disease cannot be excluded in patients without performing coronary angiography.
4- The duration of taking chemotherapy was not taken in consideration in our study.
5- The study done in a single center.

Conclusions &Recommendations:-

Conclusions: -

1-Left ventricular dysfunction was significantly diagnosed among patients with hematological malignancies treated with cytotoxic drugs.

2-Conventional 2D- and Doppler echocardiography, pulsed-wave tissue Doppler echocardiography are a reliable, simple and reproducible methods, which may be included in serial echocardiographic evaluation routinely in all patients during chemotherapy.

3- Reduction in myocardial deformation parameters (GLS) is a sign of subclinical myocardial dysfunction from chemotherapy which occur prior to any change in LVEF assessed by conventional 2D echocardiography and it is considered the most sensitive and specific parameter.

4-Parameters -such as tissue Doppler systolic velocity S` and MAPSE- can be used to detect myocardial systolic dysfunction in patients treated with chemotherapy as alternative to GLS.

5- LV systolic dysfunction occurs uniformly involving all segments of myocardium.

6- LVEF is not accurate for measuring subtle segmental LV dysfunction.

Recommendations: -

1-the GLS is recommended instead of other traditional methods for the assessment of LV systolic function in patients treated with chemotherapy.

2-In the absence of speckle tracking imaging, we should use peak systolic velocity (S') of the mitral annulus by pulsed-wave DTI and /or mitral annular displacement by M-mode echocardiography for the assessment of LV systolic function in addition to LVEF in patients treated with chemotherapy.

3-Further studies with larger sample size and longer duration are highly suggested.

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