Early detection of left ventricular dysfunction in chronic myeloid leukemia patients receiving tyrosine kinase inhibitor (Imatinib): using global longitudinal strain

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Detección temprana de disfunción ventricular izquierda en pacientes con leucemia mieloide crónica que reciben inhibidor de la tirosina quinasa (imatinib) por tensión longitudinal global

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Abstract:

Introduction: Early detection of left ventricular (LV) dysfunction and cardiotoxicity is among the documented side effects of numerous antineoplastic drugs including imatinib, which belongs to tyrosine kinase inhibitors (TKIs), administered for chronic myeloid leukemia (CML) treatment. Therefore, identification of patients at higher risk for developing LV dysfunction and cardiotoxicity would be a good strategy to reduce mortality rates.

Method: This case-control study was conducted on patients with confirmed CML, taking imatinib, referred to Babylon Oncology Center in Marjan Medical City, Babil, Iraq, between January 5th and July 1st, 2019. To this end, a special questionnaire comprised of items about patients' age, oncological and medical history of diabetes mellitus (DM), hypertension (HT), ischemic heart disease (IHD), cardiomyopathy (CMP), or heart failure (HF) along with measurement of weight, height, heart rate, and blood pressure as baseline information was employed. Echocardiographic examination was also done for case (i.e. patient) and control groups.

Results: The mean age of the patients included in this study was 43.90($\pm$13.73) years, respectively with minimum and maximum patient age of 17 and 64 years. As well, there was no difference in diastolic function of echocardiographic readings during the study. However, a significant difference was observed between the mean values of S. (cm/sec). Therefore, the systolic function could be evaluated by tissue Doppler imaging technique. There was correspondingly a significant reduction in global longitudinal strain (GLS) with preserved LV ejection fraction (LVEF). The GLS results also revealed that 60% of the patients (n=24) had normal GLS% ($\leq$-18%) and 40% of the cases (n=16) had impaired GLS% ($\geq$-17%).

Conclusion: GLS decline was observed in patients with CML receiving imatinib, compared with the control group, since they had fairly preserved or normal LVEF. Thus, GLS drop was detected without any significant reduction in EF.

Keywords: Left Ventricular, Detection, Health, Patients, Chronic Myeloid Leukemia.

Resumen:

Introducción: la detección temprana de disfunción y cardiotoxicidad del VI es un efecto secundario reconocido de muchos fármacos antineoplásicos; uno de ellos es imatinib, que pertenece al grupo TKI que se usa para el tratamiento de la LMC. La identificación de pacientes con alto riesgo de desarrollar disfunción y cardiotoxicidad del VI sería una buena estrategia para disminuir la mortalidad.

Método: un estudio de casos y controles de pacientes con LMC confirmados que están tomando el medicamento imatinib, que asisten al centro de oncología de Babylon en la ciudad médica de Marjan entre el cinco de enero y el primero de julio de 2019, un cuestionario especial utilizado incluye preguntas sobre la edad del paciente, oncológico e historial médico de DM, HT, IHD,

CMP o HF y medición de peso, altura, frecuencia cardíaca y presión arterial como información de referencia Se realizó un examen ecocardiográfico para pacientes y grupo de control.

Resultados: La edad media de los pacientes incluidos en este estudio fue de 43.90 (±13.73) años con una edad mínima del paciente de 17 años y una edad máxima del paciente de 64 años. No hay diferencia de asociación en la función diastólica de las lecturas ecocardiográficas durante el estudio. Hubo una diferencia significativa entre las medias de S ^ (cm/seg). Por lo tanto, la función sistólica puede evaluarse con tejido imaginario por Doppler. En este estudio, hubo una reducción significativa en la tensión longitudinal global con FEVI preservada, los resultados del estudio GLS fueron 60% de los pacientes (24 pacientes) tenían GL S % normal (≤ -18%) y 40% (16 pacientes) tenían deterioro GLS% (≥ -17%).

Conclusión: se observó una disminución de la tensión longitudinal global en pacientes con leucemia mieloide crónica que recibieron imatinib, al compararlos con el grupo de control, en cuanto a que tienen FEVI regular, preservada o normal. Eso nos da una idea de que la caída de GLS se detectó sin una reducción significativa en la fracción de eyección.

Palabras clave: Detección de LV, salud, pacientes, leucemia mieloide crónica.

Introduction

Chronic myeloid leukemia (CML) is known as an illness characterized by the occurrence of developed changes affecting hematopoietic stem cells (HSCs), representing 20% of leukemia in adults, whose incidence rate is by 1.6/100,000 yearly, male to female ratio (1.4/1.3), with the mean age 55 years[1].

Although there is an association between CML and radiation, cases are still seen sporadically and with no promoting factors[1]. Leukemia refers to a group of blood cancers, whose different types depend on blood cells affected, chronic mean development, and myeloid deviated from myeloid cells, which are usually developed into red blood cells (RBCs), white blood cells (WBCs), and platelets[2]. Tyrosine kinase inhibitors (TKIs) that mark the BCR-ABL gene are accordingly utilized in treatments for CML, gastrointestinal malignancies, chronic eosinophilic leukemia (CEL), and chronic lymphatic leukemia (CLL)[3]. In this respect, imatinib is mostly administered as a medication in treatment of leukemia. According to subjective explanations in clinical practices, imatinib can be sufficient for cardiotoxicity since left ventricular (LV) dysfunction progresses in some patients, accompanied by cardiac failure, worsened muscle contraction, and widened left ventricle[4].

Over the past decades, progression in cancer treatments with overall elaboration in cancer survival, cardiovascular (CV) toxicities, specifically HF, have become increasingly recognized because of introducing treatments with a diverse set of agents. Fortunately, a substantial amount of cardiotoxic effects may be preventable through careful control of known CV risk factors and use of selected cardio-protective therapy. Once LV dysfunction does occur, prompt identification and treatment can thus lead to recovery, while delayed treatment might be associated with much more limited benefits[5]. In this resepct, the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) suggest a homogeneous definition as a decrease in the LV ejection fraction (LVEF) of greater than 10%, to a value less than 53%, confirmed by a repeated study, two-three weeks after the first diagnostic imaging[6].

Cardiotoxicity denotes the direct influence of chemotherapy on the entire CV system (CVS) and to an indirect effect by a thrombogenic status or to a hemodynamic flow alteration[7]. Myocardial strain, also known as echocardiographic strain imaging or deformation imaging, also reflects LV function. According to the ASE and the EACVI, deformity changes also occur prior to ventricular dysfunction. A reduction of >15% in GLS is additionally the most informative parameter to predict cardiotoxicity, while a drop of <8% might exclude its diagnosis[8]. However, there is a grey zone between these two values[9]. It should be noted that longitudinal and radial strain increase with respect to heart rate and decline based on age range. Accordingly, echocardiographic examination of myocardial strain is a relatively new means of assessing myocardial function[10]. The present study aimed to assess the incidence of chemotherapy-induced LV dysfunction or cardiotoxicity and to identify reduction in GLS prior to fall in EF.

Method

This case-control study was conducted between January 5th and July 1st, 2019, among patients with CML, referred to Babylon Oncology Center in Marjan Medical City, Babil, Iraq. The inclusion criteria in this study were age below 65 years, diagnosis of CML, taking imatinib, normal baseline echocardiography, and fairly preserved or normal LVEF. On the other hand, the exclusion criteria were lack of an accurate assessment of GLS because of an inappropriate acoustic window, cardiac arrhythmias and/or non-sinus rhythms, moderate-to-severe heart valve disease or ischemic heart disease (IHD), cardiomyopathy (CMP), hypertension (HT), diabetes mellitus (DM), heart failure (HF), and old age. Therefore, the patients meeting the inclusion criteria were sent to do electrocardiogram (ECG) in the Echocardiography Unit in the Department of Medicine in Marjan Medical City. In the Echocardiography Unit, baseline information was recorded in the form of patient's name, age, medical history of DM, HT, IHD, CMP, or HF, smoking, and oncological history (namely, duration of disease), as well as weight and height, measured by the researcher and body mass index (BMI) and body surface area (BSA), calculated by the following equation:

BMI (Kg/m.)=wt in Kg/Ht in m^2 [11]

Echocardiographic examination was performed on the patient at rest in the left lateral position, using the Vivid E9-GE device (GE, Vingmed Ultrasound Horten, Norway), LCD 17" monitor, with image acquisition with an M5Sc transducer and harmonic imaging. All the tests were performed with the same device. Sector and depth were also adjusted to optimize the image. It should be noted that a conventional echocardiography includes pulse wave (PWD) and continuous wave (CWD), wherein PWD is used for blood velocity measurements in a specific part of interest. Its main disadvantage is aliasing that occurs in a high velocity [12]. Statistical analysis was additionally carried out using the SPSS Statistics software (version 23). Accordingly, categorical variables were presented as frequencies and percentages and continuous variables were described as mean and standard deviation (SD). Moreover, Student's t-test was utilized to compare mean scores between both study groups. To find the association between categorical variables, Chi-square (χ2) test was employed. Correlation was further practiced to evaluate relationships between continuous variables. P-value#0.05 was considered as statistically significant.

Results

In this study, 40 patients with CML meeting the inclusion criteria were enrolled, and then compared with 40 individuals in the control group. The mean age of the patients included was 43.90 ($\pm$13.73) years, respectively with the minimum and maximum patient age of 17 and 64 years. The mean duration of disease was 63.22+40.78 months, respectively with minimum and maximum duration of 6 and 156 months. The mean BMI was also by 20.5($\pm$4.1) Kg/m^2 while the mean BSA was 1.7($\pm$0.1) m^2. As well, the mean heart rate was 78($\pm$7.3) b/m, the mean systolic blood pressure was 120 ($\pm$0.7) mm Hg, whereas the mean diastolic blood pressure was 78.3($\pm$7.3) mm Hg. The mean age was different in both case and control groups. No significant difference was observed in the mean age in the case group. Moreover, there was no significant relationship between gender and cases with CML. Significant differences were additionally found between the mean values of GLS according to the study group. The mean differences of the study parameters including interventricular septum (IVS), posterior wall (PW), and LV end-diastolic diameter (LVEDD), with reference to the study groups, are presented in Tables 1 and 2.

TABLE 1:
Mean differences of age, gender, and study parameters according to study groups

Study parameters	Study group	N	Mean	SD	t-test	P-value
Age (years)	CML patients	40	43.90	13.73	1.674	0.098
	Control group	40	38.70	14.04		

	CML patients	Control group	χ^2	P-value		
Gender Male Female Total	26 (65.0) 14 (35.0) 40 (100.0)	24 (60.0) 16 (40.0) 40 (100.0)	0.21	0.644		

Study parameters	Study group	N	Mean	SD	T-test	P-value
E (cm/sec)	CML Control	40 40	83.35 66.75	22.34 10.11	4.28	<0.01
A (cm/sec)	CML Control	40 40	68.40 58.12	26.01 17.01	2.09	0.04
E/A	CML Control	40 40	1.22 1.16	0.41 0.21	0.792	0.431
E/e^	CML Control	40 40	7.82 6.22	2.35 1.72	3.465	0.001*

P-value#0.05 (significant)

TABLE 2
Differences in study factors according to study groups

STUDY PARAMETERS	STUDY GROUP	N	MEAN	SD	T-TEST	P-VALUE
GLS (%)	CML	40	-17.73	2.49		
	Control	40	-19.55	2.24	3.421	0.001*
IVS (mm)	CML	40	9.02	1.13	-0.349	0.728
	Control	40	9.10	0.90		
PW (mm)	CML	40	8.57	1.02	-0.727	0.469
	Control	40	8.75	1.12		
LVEDD (mm)	CML	40	46.70	4.16	0.262	0.794

P-value#0.05 (significant)

There were mean differences in EF (%) in the patient group (CML group). Significant differences between the mean values of EF according to the study group are presented in Figure 1 (t=-2.067, P=0.042*). There were also mean differences in E^ (cm/sec) between the patients with CML and the control group. However, no significant differences were found between the mean values of E^ (cm/sec) according to the study groups, as illustrated in Figure 2 (t=0.29, P=0.773). Given the mean differences of S. (cm/sec) according to the study groups, significant differences were observed between the mean values of S. (cm/sec), depicted in Figure 3 (t=-2.139, P=0.036*).
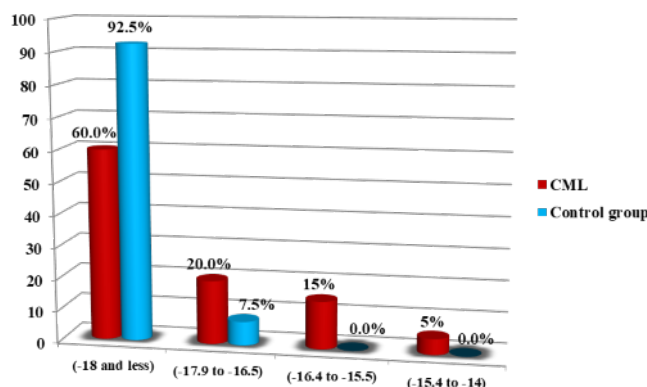
FIGURE 1:
Relationship between GLS and study groups

There was a significant relationship between GLS and study groups (P=0.002*).
Figure 2:
Figure 3:
The study results revealed that 60% of the patients (n=24) had normal GLS% (≤-18%) and 40% of the cases (n=16) had impaired GLS% (≥-17.9%). Furthermore, dividing the patients having GLS% above -17.9% demonstrated that 20% of the cases (n=8) were between -17.9% and -16.5% and 15% of the patients (n=6) were between -16.4% and -15.5%. Moreover, the remaining 5% of the cases (n=2) were between -15.4 and -14%. Accordingly, comparison of the results with those in the control group showed a significant correlation (p=<0.05), as presented in Figure 1.

DISCUSSION

LV dysfunction is a remarkable complication of chemotherapy-induced treatments with contrary effects from the perspective of clinical outcomes. In this study, there were low morbidity profiles and risk factors of cardiac impairments were relatively low, the mean age of the patients was 43.90 (±13.73) years and their mean BMI was 20.5(±4.1) kg/m^2. The patients concerned had no history of DM, HT, IHD, CMP, as well as arrhythmia and smoking. With regard to oncological history, the patients had CML, receiving TKIs (i.e., imatinib medication) tablets 400mg/day, similar to the doses prescribed in other studies [13]. The incidence rate of cardiac impairment in a systematic review published in 2014 had been between 13 and 32% [14]. Several studies in the United States in 2011 [15] and 2013 [16] had further found an incidence rate of 20%.

It should be noted that myocardial deformation occurs earlier than changes in LVEF [14]. Longitudinal strain is thus the most important method used for the assessment of the LV than the LVEF function. Many studies have also shown a difference in GLS and LVEF for diagnosed cases and minor decrease in LV function [17,18]. According to these studies, GLS as well as segmental strain have good ability than LVEF to detect the size of infarction and segmental movement in patients with myocardial infarction (MI) [17,18]. An association between GLS and LVEF has also led to detection of a growth in normal individuals compared with patients with MI and cardiac failure [19]. In this resepct, 40-80 frame/sec is suggested [20]. Increase in pulse rate and low frame can thus result in underneath cases wherein systolic measures are lost, subsequent to low estimation of real deformity [21]. The present study indicated that GLS was more similar to echocardiographic image quality once compared with LVEF. In this study, the distribution of the patients with CML according to LV function was assessed by GLS%. In this sense, there was a significant reduction in GLS with preserved LVEF but no clinical significance related to LV dysfunction was observed. Thus, comparing the results with

the control group, a significant correlation was detected (p=<0.05), accounting for the sensitivity of GLS in early detection of LV impairment before the development of LVEF impairment. In line with the present study results, Negishi et al. had stated that the use of GLS was important in diagnosis of LV [22]. Kerkelä et al. had also described the active dysfunction of LV through imatinib therapy on 10 patients [23]. They had suggested that the cardiotoxic effects of imatinib could be mediated via inhibition of c - Abl signaling passageways, expecting the development of peripheral edema and fluid retention [24]. Moreover, it had been reported that individuals treated with imatinib had developed severe congestive heart failure (CHF) due to myocyte contractile dysfunction [25]. Cardiotoxicity of imatinib may thus range from asymptomatic subclinical abnormalities such as electrocardiographic changes and LVEF fall to life-threatening events like congestive heart failure and acute coronary syndromes that may happen due to incidence of arterial thrombotic and arterial occlusive events [26]. Early initiation of heart failure treatment accordingly seems important for the recovery of the LV function in patients undergoing a significant reduction in LVEF due to chemotherapy [27]. Therefore, early identification of impaired systolic function is of utmost importance. In the present study, the findings revealed that E/E. mean value had significantly grew, which was considered as the initial indicator of diastolic loss function [28]. Another study had correspondingly demonstrated high E/E. ratio associated with high pressure of filling in LV [29]. Of note, there were significant differences among S. mean values, so the systolic longitudinal function could be simply measured by tissue Doppler imaging technique. The significant decrease in S. diagnosis immediately after three months post-chemotherapy is accordingly vital to detect deterioration in LVEF after six months [30]. Thus, low S. can be seen in symptom-free patients with a history of chemotherapy, numerous years before no deterioration in LVEF [31].

CONCLUSION

GLS decline was observed in patients with CML receiving imatinib, as compared with the control group, since they had fairly preserved or normal LVEF. Therefore, GLS drop could be detected without any significant reduction in EF.

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