Global Longitudinal Strain of Chronic Granulocytic Leukemia Patients treated with Imatinib and Nilotinib

Indra Wijaya,[1] Arief Sumarna,[1] Eliza Nurazizah,[2] Evan Susandi,[3] Erwan Martanto[1]

[1]Department of Internal Medicine, Faculty of Medicine Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital Bandung, Indonesia
[2]Faculty of Medicine Pasundan University Bandung, Indonesia
[3]Faculty of Medicine Universitas Padjadjaran, Indonesia

pISSN: 2302-1381;
eISSN: 2338-4506;
http://doi.org/10.15850/ijihs.v9n2.2217
IJIHS. 2021;9(2):49–54

Received:
November 23, 2020

Accepted:
September 30, 2021

Abstract

Objective: To determine left ventricular function of patients with Chronic Granulocytic Leukemia in Chronic Phase (CGL-CP) who received imatinib and nilotinib by using Global Longitudinal Strain (GLS) examination.

Methods: This was a descriptive study involving 46 CGL-CP patients who received imatinib and nilotinib therapy at the Hemato-Oncology Clinic of the Internal Medicine Departement of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. Sampling was performed consecutively during the period of October to December 2019. Variables assessed in this study were age, gender, BMI, length of treatment, hemoglobin level, Left Ventricular Ejection Fraction (LVEF) value, and Global Longitudinal Strain (GLS). Primary data were tested for normality using the Saphiro-Wilk test. Statistical analysis was performed using SPSS software version 25.0.

Results: Thirty-nine patients (seventeen males and twenty-two females with a mean age of 42±11) who had been in therapy for about 8 to 179 months at the time of the study were included as subjects. On average, the GLS results for both treatment groups indicated a normal value based on the classification of the American Society of Echocardiography. The imatinib group gained a score of -22.4% (average range= -16.4% to (-28.1%)), while the nilotinib group gained a score of -21.6% (average range = -18.0% to (-25.9%)).

Conclusion: This study described the left ventricular function based on results of GLS in CGL-CP patients receiving imatinib and nilotinib.

Keywords: Chronic granulocytic leukemia, global longitudinal strain, imatinib, left ventricular ejection fraction, nilotinib

Introduction

Chronic granulocytic leukemia (CGL) is a myeloproliferative disorder caused by uncontrolled expansion of pluripotent hematopoietic cells, ranging between 10 and 15 cases/ 10^6/year without any significant geographic or ethnic differences.[1] In Indonesia, the incidence of CGL is unknown. In 2017, 301 patients went to the Hemato-Oncology Polyclinic of Internal Medicine Department in Hasan Sadikin, Bandung.[2]

Tyrosine Kinase Inhibitor (TKI) is the standard treatment for CGL.[3] Currently, in Indonesia, only imatinib and nilotinib are available. Imatinib is given as the first choice, while nilotinib is given when there is resistance or intolerance to imatinib.[4] The cardiotoxic effect on TKI is one of the rarely reported events. According to some literature, the incidence of these effects varies from 0.5 to 2%.[5–7] In this study, ten individuals who developed severe congestive heart failure

Correspondence:
Indra Wijaya,
Department of Internal Medicine, Faculty of Medicine Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital Bandung, Indonesia,
e-mail: indrawijayaipd@gmail.com

while on imatinib and this study show that imatinib-treated mice develop left ventricular contractile dysfunction. Transmission electron micrographs from humans and mice treated with imatinib show mitochondrial abnormalities and accumulation of membrane whorls in both vacuoles and the sarco- (endo- The variations range from the asymptomatic lengthening of the QT interval, palpitations, arrhythmia, pericardial effusion, congestive heart failure, acute coronary syndrome and myocardial infarction.[8,9]

A previous study showed that the incidence of cardiovascular events is higher in nilotinib as compared to imatinib-related patients.[10] Experts currently advise against using nilotinib in patients with a high-risk cardiovascular profile whenever possible. Among other TKI, imatinib is the least associated drug with cardiac failure.[11]

Cancer therapy–related cardiac dysfunction is commonly defined as a decrease in left ventricular ejection fraction (LVEF) using two-dimensional (2D) echocardiography.[12] Strain rate on LVEF examination is a parameter that depends on the heart's workload, and the diagnosis of cardiac dysfunction associated with cancer drug administration is often found at an advanced stage when the impairment of heart function has become irreversible. It is calculated using the modified biplane Simpson method, depends on operator experience, and is not sufficiently sensitive to detect subclinical myocardial dysfunction.[12,13] Patients underwent complete echocardiography on four occasions: baseline (V1).

Global longitudinal strain (GLS) is the best strain parameter for assessing left ventricular systolic function due to being more sensitive than LVEF. It also can be used to identify subclinical left ventricular systolic dysfunction in cardiomyopathy.[14] GLS assessment is independent of cardiac workload; it is a sensitive method for detecting subclinical ventricular dysfunction before LVEF is reduced in ejection fraction patients treated for various types of cancer.[12]

Therefore, this study aimed to explore the left ventricular function by using GLS in CGL-CP patients receiving imatinib and nilotinib.

Methods

This study received approval from the Health Research Ethics Committee of Hasan Sadikin General Hospital number LB.02.01/X.6.5/303/2019. This descriptive cross-sectional study involved 44 CGL-CP patients, selected based on the patient's arrival from October to December 2019 at the Hemato-Oncology Polyclinic of Internal Medicine Department in Hasan Sadikin, Bandung, who received imatinib and nilotinib. The study excluded patients with a past medical history such as hypertension, diabetes mellitus, and heart defects treated before receiving imatinib and nilotinib.

The variables included in this study were age, gender, BMI, duration of treatment, hemoglobin value, LVEF value, and GLS value. Subsequently, the subjects were examined by standard 2D transthoracic echocardiography followed by left ventricular GLS. Two consultant cardiologists assessed this examination with GLS echocardiography competency. The GLS examination on the left ventricular used the speckle tracking echocardiography (STE) technique, while the LVEF measurement used the Simpson biplane method obtained from 2 and 4-chamber apical views. The average GLS % in normal healthy populations, according to the American Society of Echocardiography (ASE), is -20%.[15]

The normality of primary data was analyzed using the Shapiro-Wilk test. Statistical analysis was performed using SPSS software version 25.0.

Results

There were 39 patients included in this study (Table). Seven of forty-six CGL-CP patients were excluded from the study due to the poor echocardiography window. The findings based on the normality test results using Shapiro Wilk analysis found that the distribution of the variables of age, hemoglobin level, GLS%, and LVEF% were normal ($p>0.05$). Meanwhile, the length of therapy distribution was not normal ($p <0.05$).

The average LVEF was 66%, with a standard deviation of 5%. In the imatinib therapy group alone, it was 66%, with a standard deviation of 5%. In the nilotinib group it was 65%, with a standard deviation of 4%.

The average GLS% in 39 subjects showed -22.1%, with standard deviation of 2.9%. The average size in the group of patients treated with imatinib alone was -22.4%, with a standard deviation of 3.0%, while in the group of patients treated using nilotinib was -21.6%, with a standard deviation of 2.6%. The average GLS %, according to American Society of Echocardiography (ASE) guidelines, was within normal limits. There were two subjects with a decrease in the percentage of GLS with

Table 1 Subjects Characteristics

Variable	Total n=39	Therapy Group	
		Imatinib n=28	Nilotonib n= 11
Age (y.o.). mean ±SD	42±11	42±11	41±12
Gender. n (%)			
Male	17 43.6)	10 (35.7)	7 (63.6)
Female	22 (56.4)	18 (64.3)	4 (36.4)
BMI (kg/m^2). Median (Range)	25.1 (19.6–35.9)	24.9 (20.7-35.9)	26.0 (19.6-35.9)
BMI Criteria. n (%)			
Normal	10 (25.6)	6 (21.4)	4 (36.4)
Overweight	8 (20.5)	8 (28.6)	0 (0.0)
Obesity I	18 (46.2)	12 (42.9)	6 (54.5)
Obesity II	3 (7.7)	2 (7.1)	1 (9.1)
Duration of Therapy (month). Median (Range)	41 (8-179)	39 (8-179)	47 (14-143)
Hemoglobin. mean ±SD	12.1 ± 1.7	11.8 ± 1.5	13.9 ±1.9

a value of -16.4% and -16.6%. (Fig.)

Discussion

The age of CGL-CP patients in this study ranged from 26 to 61 years old, consisting of more women (56.4%) than men (43.6%). Wing *et al*. mentioned in their journal that the average age of CGL patients in the United States is 65 years, in China is 45-50 years, Thailand is 36-38 years, India is 38-40 years, and 37 years in South Korea. Reksodiputro *et al*.[16] studied the epidemiological studies, and mutation profiles of CGL patients in Indonesia mentioned that 100 patients were evaluated between January 1st, 2009, to December 31st, 2011, and found that the average age was 34-35 years, and more patients were of productive age.The International Randomized Study of Interferon and STI571 (IRIS) showed that CGL is more common in the elderly group and very different from the age group of CGL patients in Indonesia. Although the description looks different from Caucasian, the age of CGL patients in Indonesia is more similar to the data in Asia.[16]

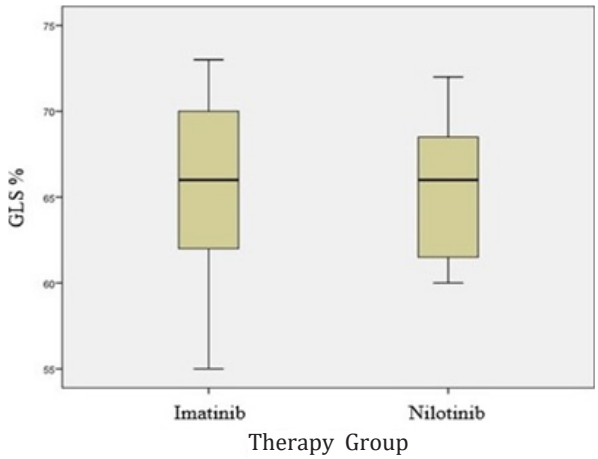

Fig. Boxplot Difference in GLS% between Imatinib and Nilotinib Therapy Groups

The study's average LVEF and GLS results of CGL patients receiving imatinib and nilotinib therapy were within normal limits. Taher *et al*.[17] previously reported no change in echocardiographic LV function after using imatinib for one year in 50 CGL patients. In addition, Cirmi *et al*.[18] also reported that among other TKIs, it is the least likely to be associated with cardiac failure.Fransisco *et al*.[20] studied the cardiac function of patients with CGL receiving imatinib and nilotinib with a global longitudinal strain examination at the start of therapy. After one year of therapy, the results are normal; however, these results should be confirmed by a multicentre study. In this study, the average percentage of GLS in CGL patients who received imatinib was within normal limits, but there were two subjects with a decrease in the percentage of GLS with a value of -16.4% and -16.6%.

The first subject with a decreasing GLS percentage result was a 45-year -old man with a BMI of 23.4 who received imatinib for 74 months, no comorbid, hemoglobin level was 15.4, and LVEF 69% with GLS -16.6%. The duration of imatinib administration influenced the possibility of decreasing GLS in this subject. He has received imatinib for 74 months, but it still needed to be evaluated for certainty cause of the decrease in the GLS percentage. The researchers did not have a baseline of GLS values before getting imatinib therapy.

The second subject with a decreasing GLS percentage result was a 32-year-old woman with a BMI of 27.3, and obese I. She has received imatinib for 29 months, no comorbid, hemoglobin level was 13.1, and LVEF 58% with GLS -16.4 The possibility of decreasing GLS in this subject was influenced by the duration of giving imatinib, which was more than seven months, and increased BMI. Obesity is associated with lower strain scores in children and adults without other comorbidities or decreased left ventricular ejection fraction.[19]

According to the Food and Drug Administration (FDA), the use of imatinib has an elimination time in the body of 7 days and its cardiotoxicity is reversible.[21] In CGL patients receiving nilotinib with a history of previous use of imatinib, but no reduction in GLS, the cardiotoxic effects of imatinib were lost due to the elimination time of imatinib. Unfortunately, we did not have baseline ECG or echocardiography data before TKI therapy. In this study, the group of CGL-CP patients using nilotinib were patients who had received imatinib treatment, so the effect of previous imatinib treatment might have a biased effect on the study results. However, the results did not find any cardiotoxic effects in the nilotinib group.

More than 10% of the samples were excluded due to a poor echocardiography window. Various factors can affect the GLS measurement results. These various factors can be divided into technical factors and clinical factors. Technical factors are usually related to the automation of tools, including image quality, image selection, segmentation model selection, selection of areas to be analyzed, timing in the cardiac cycle, poor tracking, and differences between software in performing data analysis. Clinical factors include age, gender, systolic blood pressure, type 2 diabetes mellitus, and obesity.[22] The limitation of this study is that there are no data on the causes of poor echocardiography windows in patients.

In this study, 16 patients who received imatinib therapy were categorized as obese I and two patients categorized as obese II. This study did not have the baseline BMI data before the initiation of TKI; therefore, this study could not conclude whether the imatinib caused the weight gain in our samples. However, a previous study by Aduwa *et al*.[23] reported that imatinib induces significant weight gain and BMI modification after 24 months.The mechanism by which imatinib causes weight gain is still unknown. The hypothesis is that weight gain in patients treated with imatinib may be associated with a complex mechanism involving platelet-derived growth factor receptor kinase tyrosine phosphorylation.[23]

This study has determined the left ventricular function by using GLS in CGL-CP patients receiving imatinib and nilotinib.

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