Sys Rev Pharm 2020; 11(3): 657 – 660
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

The Correlation of Imatinib Therapy Duration and Estimated Glomerular Filtration Rate in Chronic Myeloid Leukemia Patients

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Article History: *Submitted: 12.01.2020* *Revised: 21.02.2020* *Accepted: 26.03.2020*

ABSTRACT

Chronic myeloid leukemia (CML) is a chronic myeloproliferative disease. Treatment of CML with TKI may cause changes in glomerular filtration rate (GFR) over time. The objective of the study was to analyze the correlation of imatinib therapy duration and eGFR in CML patients in outpatient clinic of Dr. Soetomo Hospital, Surabaya. This was an observational analytic cross-sectional study. The duration of imatinib therapy was more than three months and estimated glomerular filtration rate (eGFR) as measured using the CKD-EPI creatinine equation. Among the 64 subjects studied, most of them were male as many as 76.6%. The mean age was 41.36 years. The mean serum creatinine level was 0.959 mg/dL. The mean eGFR was 93.184 mL/min/1.73m2. The mean duration of therapy for imatinib was 30.66 months. There was a significant inverse relationship between the duration of imatinib therapy and eGFR ($r = -0.470$; $p < 0.001$). There was a significant negative correlation between the duration of imatinib therapy with eGFR in CML patients.

Keywords: Duration of imatinib therapy, estimated glomerular filtration rate (eGFR), CML patients

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DOI: 10.31838/srp.2020.3.88

INTRODUCTION

Chronic myeloid leukemia (CML) is a malignancy of the sixth-highest, reaching 15% of all blood malignancies in adults .(1) CML is affected by various risk factors, they are radiation exposure, age, and sex. In addition, CML patients are high risk of the infections .(2) CML has undergone a revolution in terms of therapy, where previously with therapy using conventional chemotherapy (busulfan, hydroxyurea, and IFN-α), but now imatinib, which is the first-generation tyrosine kinase inhibitor (TKI) that is successfully used in clinical medicine that not only produces effects beneficial therapy but also fewer side effects compared to previous standard therapies.(3,4) Initially, the use of imatinib was considered not to cause interference with kidney function.(5,6) The kidney function represents by Glomerular filtration rate (GFR) because of glomerulus act as a filter.(7,8) When normal kidney function is reduced, ultrafiltration will be required to maintain volume control.(9) Identification of kidney function is important because it is associated with high morbidity and mortality.(10) Although the results of subsequent studies showed that imatinib could affect kidney function,(11,12) the effect of imatinib on kidney function, namely a decrease in GFR, is still not fully studied.

Since the use of imatinib in 2000, the mortality rate of CML patients has decreased from 10-20% to 1-2%.(13) The government-borne costs associated with the treatment of imatinib in CML patients at America union are $ 71,292 per year.(14) Besides, CML also causes a decrease in the quality of life of patients.(15) If the decline in kidney function due to the use of imatinib in CML treatment is not immediately anticipated, then it can increase the morbidity of CML patients, increase the cost of care to be incurred and decrease the quality of life of CML patients. So, it is necessary to research the side effects of imatinib on kidney function in CML patients.

Treatment with imatinib in CML patients has a risk of developing kidney side effects in the form of a decrease in GFR, which can cause kidney disorders.(11) If kidney function is interrupted by any cause, the kidneys will not be able to maintain normal physiological functions.(16) Therefore, it is important to monitor the kidney function of CML patients receiving imatinib therapy. These kidney side effects may be caused by several mechanisms, including toxic tubular damage and tumor lysis syndrome (TLS). Also, PDGF receptors (which are inhibited by imatinib) are important in regenerating renal tubular cells after acute tubular necrosis.(17) According to a previous study showed 7% of patients had acute kidney injury, and 12% of patients experienced chronic kidney failure due to the use of imatinib.(11) While the other studies found that 4% of patients had acute kidney injury and 14% of patients developed CKD when receiving migrant workers, especially imatinib. The decrease in kidney function that occurred is related to the duration of therapy imatinib.(12)

Until now, the research that explains the effect of TKI therapy, especially imatinib on GFR in patients with CML in Indonesia, has not been fully studied, and the data are still lacking, so that further evaluation is needed. Based on the explanation above, the researchers examined the link between the duration of imatinib therapy to renal function in CML patients who received imatinib therapy, especially in the scope of Dr. Soetomo Teaching Hospital, Surabaya.

METHODOLOGY

This was an observational analytic study with a cross-sectional design carried out in the hematology – medical oncology outpatient installation of Dr. Soetomo Teaching

Hospital, Surabaya. The population of this study was CML patients receiving imatinib therapy. The study sample was collected by consecutive sampling technique.

Inclusion criteria included ages 18-60-year patients who were willing to take part in the study and patients who get imatinib therapy for at least 3 months. Patients with kidney disorders before receiving imatinib therapy, diabetes mellitus, hypertension, infections, obstruction nephropathy and patients with the use of nephrotoxic drugs were excluded from the study. This study had obtained ethical feasibility from the ethics committee of Dr. Soetomo Teaching Hospital, Surabaya.

Sample Collection

Duration of Imatinib Therapy was the length of time patients get imatinib from hematology–medical oncology outpatient installation since the diagnosis of CML had been established. It was calculated in units of months. Data collection was obtained from a history matched with medical record data. The duration of this study was in patients who had received therapy for more than 3 months.

Calculation of estimated glomerular filtration rate (eGFR) was done by inserting serum creatinine data into the formula using the CKD-EPI creatinine equation method (KDIGO, 2012). Serum creatinine levels were the levels of creatinine circulating in blood serum. Taking serum blood examinations was carried out study subjects. The results of the examination were stated in mg/dL.

Statistical Analysis

Correlation of duration of imatinib therapy with eGFR was calculated using the Pearson parametric test because data distribution was normal. The correlation test output was expressed by the p-value, the direction of correlation, and the correlation coefficient (r). The value of $p < 0.05$ was stated to be statistically significant. The direction of negative correlation means that the higher the value of the independent variable, the lower the value of the dependent variable. The magnitude of the correlation is stated to be very weak (r = 0-0.2), weak (r = 0.2-0.4), moderate (r = 0.4-0.6), strong (r = 0.6-0.8), and very strong (r = 0.8-1.0) .

RESULTS

The sample of this study was a total of 64 people who met the inclusion and exclusion criteria. The mean age was 41.36 years with the youngest age range of 18 years and the oldest age of 60 years. The male subjects were 76.6%, and female were 23.4%. The conditions of the general characteristics of the research subjects are shown in Table 1.

Based on the duration of imatinib therapy for CML patients in this study, it was found that the distribution of the duration of imatinib therapy was normal, with mean of 30.66 months. All research subjects were examined for serum creatinine levels, then eGFR was calculated by entering serum creatinine values into the CKD-EPI formula. Based on the results of the eGFR examination in 64 subjects of CML patients, it was found that the distribution of normal eGFR values, with mean eGFR of 93.184 mL/min /1.73m^2 (Table 3).

Both variables were tested for normality, and the results were normally distributed. Correlation between duration of imatinib therapy and eGFR was performed using Pearson parametric test. The results of the Pearson correlation test obtained $p < 0.001$ and coefficient correlation (r) of -0.470. There was a significant correlation between the duration of imatinib therapy and eGFR ($p < 0.05$) with the strength of the moderate negative correlation (r = -0.470). This means that the longer the duration of imatinib therapy, the lower the eGFR. The correlation scatters diagram of the two variables is shown in Figure 1.

DISCUSSION AND CONCLUSION

Treatment of CML with TKI causes changes in renal function. This study found that the duration of imatinib therapy was significantly correlated with eGFR with moderate negative strength. This means that increasing the duration of imatinib therapy in CML patients can lower the value of eGFR.

Most patients with CML tended to receive TKI treatment for a long time and maybe indefinite. Thus, it is important to understand the long-term consequences of exposure to these drugs to patients, especially their effects on kidney function. It is important to monitor kidney function, especially during therapy.(12) Imatinib therapy in CML patients in non-clinical trials is associated with acute kidney injury, which is most often irreversible, and long-term care is associated with a clinically relevant reduction in eGFR, which can cause chronic kidney failure. However, a significant decrease in eGFR associated with the duration of imatinib therapy does not depend on other factors, such as age, hypertension, diabetes, underlying chronic kidney failure, and previous treatment. Evaluation of the long-term effects of imatinib exposure is very important because the duration of optimal therapy in CML patients has not been determined, and discontinuation of treatment is not recommended because of the potential for relapse. Furthermore, the kidney function of patients undergoing imatinib therapy must be monitored regularly.(11,18)

Treatment with imatinib in CML patients has the risk of developing kidney side effects in the form of a decrease in GFR, which can cause acute kidney problems after more than three months of treatment. Whereas, long-term treatment can cause a significant reduction in GFR, which will result in chronic kidney failure.(11,18) However, the molecular mechanism behind imatinib-induced nephrotoxicity has not been fully explained.(17)

The correlation between duration of therapy and eGFR in our study was in line with previous studies. However, studies examining the relationship between the duration of imatinib therapy with eGFR have not been carried out. The previous study that examined the relationship between the duration of imatinib therapy with the eGFR available, with results almost the same as our study, which obtained a correlation between the duration of imatinib therapy with eGFR.(11,12) That study of 105 CML subjects presented a correlation value of r of = -0.368 with P <0.0001. These studies showed a relationship with a weak correlation strength.(11) Whereas, our study revealed that there was correlation with moderate strength. This can be because in

our study, we have excluded confounding factors that influence eGFR.

The results of this study indicate a significant negative correlation between the duration of imatinib therapy with eGFR. Thus, long-term imatinib treatment affects the kidney function of CML patients, and it is necessary to increase alertness by periodically evaluating kidney function.

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TABLES

Table 1. Characteristic of Subjects

Variables	Mean±SD
Sex (n)	
Male	49 (76.6%)
Female	15 (23.4%)
Age (Years)	41.36±13.162
IMT	23.113±3.558
Duration of therapy	30.66±21.102
Hb	12.575±1.9336
BUN	
Median	10 (5-21)
Creatinine serum	0.959±0.1578
eGFR	93.184±19.7874

Table 2. Results of Pearson's analysis of duration of therapy with eGFR

	Egfr		note
	R	p	
Duration of therapy	-0.470	<0.001	meaningful

FIGURE

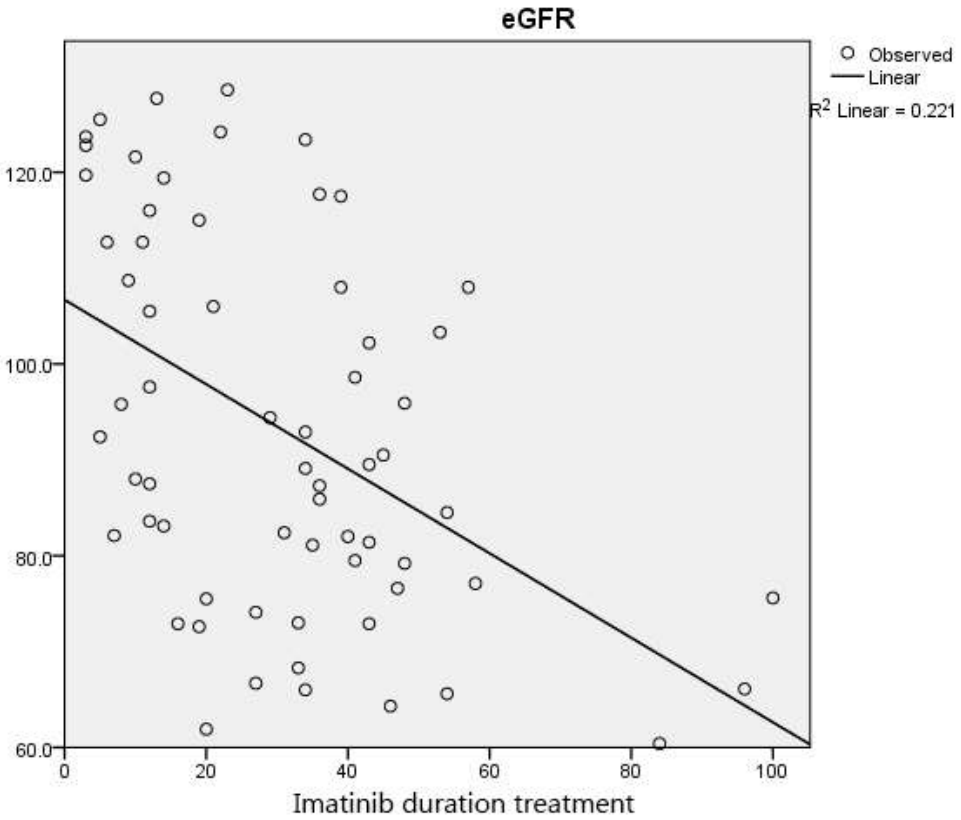

Figure 1. Scatter diagram of correlation of duration of imatinib therapy with eGFR.