Relationship between trough level of tyrosine kinase inhibitor (imatinib and nilotinib) and BCR-ABL ratios in an Indonesian chronic-phase chronic myeloid leukemia (CML) population

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Abstract

Objectives: Among Chronic Myeloid Leukemia (CML) patients treated with Tyrosine Kinase Inhibitor (TKI-imatinib-nilotinib), some showed a suboptimal response. Based on pharmacokinetic studies, TKI trough level (C^{∞}_{min}) is associated with clinical outcomes, reflected by the BCR-ABL ratio. However, the interindividual pharmacokinetic variability of imatinib and nilotinib is found to be moderate–high. This study aims to analyze the relationship between TKI C^{∞}_{min} and BCL-ABL ratio in chronic-phase CML patients.

Methods: Cross-sectional study to CML chronic-phase patients treated with imatinib 400 mg daily or nilotinib 400 or 800 mg daily for ≥12 months. The exclusion criteria were therapy discontinuation within 29 days (imatinib) or 8 days (nilotinib) before the sampling day. Blood samples were drawn 1 h before the next dose. Imatinib-nilotinib C^{∞}_{min} and BCR-ABL ratio were measured using HPLC and RT-qPCR. The relationship was analyzed using bivariate correlation Spearman's rho test.

Results: Twenty-three imatinib and 11 nilotinib patients met the inclusion criteria. The mean imatinib and nilotinib C^{∞}_{min} were 1,065.46 ± 765.71 and 1,445 ± 1,010.35 ng/mL respectively. There were large interindividual variations in both groups (71.87% vs. 69.88%). Half of the patients in each group were found to reach C^{∞}_{min} target (≥1.000 ng/mL, imatinib; ≥800 ng/mL nilotinib), but only 12 (35,29%) of them result in BCR-ABL ratio ≤0.1%. C^{∞}_{min} imatinib was found to be significantly associated with BCR-ABL ratio. But, not with the nilotinib group.

Conclusions: There were high interindividual variations of imatinib and nilotinib correlated with BCR-ABL ratio, but no correlation in nilotinib.

Keywords: BCR-ABL ratio; C^{∞}_{min}; CML; imatinib; nilotinib.

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Introduction

The development of tyrosine kinase inhibitors (TKI) has changed the management of Chronic Myeloid Leukemia (CML) therapy from lethal cancer to controlled chronic disease [1, 2]. Imatinib and nilotinib selectively inhibit tyrosine kinase activity by occupying the Adenosine Tryphosphate (ATP) binding domain in ABL so as to prevent substrate phosphorylation. The inhibition of phosphorylation of the substrate will inactivate the nucleus and cytoplasmic signal transduction pathways, including RAS, phosphatidylinositol-3 kinase – alpha serine/threonine kinase (PI3K-Akt) and Janus kinase – signal transducers and activators of transcription (JAK-STAT) which cause a decreased proliferation and increased cell apoptosis [3].

Imatinib mesylate is the first generation of TKI, which can induce therapeutic responses including hematological response (leucocyte), cytogenetic response (presence/absence of cells containing the Philadelphia chromosome), and molecular response (BCR-ABL ratio) in more than 80% of CML patients [4, 5]. Although imatinib is known to produce a high cytogenetic response, some patients do not respond to imatinib therapy or relapse after a primary response. Nilotinib is one of the second generation TKI that is approved by the FDA to be used as therapy in CML patients who are resistant or intolerant to imatinib [6, 7].

The BCR-ABL ratio is a parameter of the TKI molecular response, expressed the ratio of BCR-ABL transcription

level to ABL with a target of ≤1% after 12 months of therapy. CML patients treated with imatinib or nilotinib showed that decreasing of BCR-ABL transcript levels occurred most rapidly in 6 months on TKI and reached the plateau at 12–15 months after therapy [8]. Data in Dr. Soetomo General Hospital, Surabaya, showed that there was an increase in CML cases from 58 patients in 2006 to 160 patients in 2014 [9] and molecular response attained in 40% patients only.

Based on pharmacokinetic studies, there is a relationship between of TKI C_{min}^{∞} and therapeutic response [10]. Additionally, there was high variability in TKI C_{min}^{∞}. The coefficient of interindividual variation in C_{min}^{∞} of imatinib and nilotinib is 45–50% [11]. One of the factors that influence the suboptimal response to TKI therapy is the variation of pharmacokinetic factors and/or drug interactions that affect the pharmacokinetics of TKI [12]. This study was conducted to determine the relationship between the TKI C_{min}^{∞} (imatinib and nilotinib) and BCR-ABL ratio in patients with chronic phase CML who had used TKI, either imatinib or nilotinib, for ≥12 months therapy.

Materials and methods

Study design and population

This observational study was conducted on adult patients (age ≥18 years) with a diagnosis chronic phase CML who had been treated with TKI, both imatinib 400 mg/day or nilotinib 400 or 800 mg/day for ≥12 months. The exclusion criteria were the discontinuation of therapy within 29 days (imatinib) or 8 days (nilotinib) before the sampling day. All subjects gave informed consent before the study. The study was approved by Dr. Soetomo General Hospital Ethical Review Committee and conducted in accordance with the criteria set by the declaration of Helsinki.

Study protocol

About 8 mL of blood was drawn from each patient within ±1 h before the next dose. Blood samples were collected in two separate vacutainers for determination of C_{min}^{∞} TKI (5 mL) and BCR-ABL ratio (3 mL). Imatinib and nilotinib levels were measured using High-Performance Liquid Chromatography (HPLC) method, and the BCR-ABL ratio is measured using RT-qPCR.

Measurements of C_{min}^{∞} of imatinib and nilotinib

Trough levels of imatinib and nilotinib in plasma were measured by the HPLC method. About 500 µL of plasma added, then 500 µL acetonitrile and 100 µL of the internal standard solution with a concentration of 50 µg/mL in methanol (the internal standard used for imatinib assay was nilotinib, and for nilotinib assay was imatinib), then centrifuged 6,000×g for 10 min. The supernatant obtained was evaporated to dryness with N_2 gas, then resuspended in a 500 µL mobile phase, and then injected into the HPLC column. The instrument used was the DAD-Agilent 1100 series HPLC machine with RP-C18 columns. The mobile phase used consisted of 40% solvent A (72.5% water, 25% methanol, and 2.5% triethylamine), 20% methanol, and 40% acetonitrile, which was flowed at a rate of 0.9 mL/min at 35 °C and isocratic conditions. Eluation was observed at wavelengths of 267 nm [13].

Measurements of BCR-ABL ratios

Three mL of blood sample collected in EDTA vacutainer was stored at a temperature of 2–8 °C and processed within 48 h of the initial sampling to avoid degradation of RNA. Measurements of the BCR-ABL ratio in whole blood CML patients were carried out by the RT-qPCR method with the GeneXpert tools. The cartridge preparation process must be carried out within 15 min.

Statistical analysis

The relationship between the imatinib/nilotinib C_{min}^{∞} and BCR-ABL ratio was analyzed by the bivariate correlation Spearman rho test.

Results

Twenty-three imatinib patients and 11 nilotinib patients met the inclusion criteria and signed informed consent. All subjects in the nilotinib group had a history of being treated with imatinib before being treated with nilotinib. Other patient characteristics data are presented in Table 1.

There were 10 (43.48%) patients who used imatinib could reach the C_{min}^{∞} target (>1,000 ng/mL). In the nilotinib group, there were 7 (63.64%) patients could achieve the C_{min}^{∞} target (>800 ng/mL). The distribution of C_{min}^{∞} from the two groups is presented in Figure 1.

Table 2 shows that the average C_{min}^{∞} is 1,065.46 ± 765.71 ng/mL for imatinib and 1445 ± 1,010.35 ng/mL for nilotinib. The data showed there were large interindividual variations in both groups (71.87% vs. 69.88%).

The distribution of the BCR-ABL ratio values of the two groups is shown in Figure 2.

Ten (43.48%) patients who received imatinib achieved BCR-ABL ratio of ≤0.1%, while in nilotinib group achieved in 7 (63.64%) patients.

Within imatinib group, there was a correlation between C_{min}^{∞} and BCR-ABL ratios (p=0.043) and the mean of C_{min}^{∞} in the group of patients who had a BCR-ABL ratio ≤0.1% tended to be greater than the group of patients who had a BCR-ABL ratio of >0.1% (1,381.95 vs. 822.01 ng/mL) (Table 3). In addition, the group of patients who had C_{min}^{∞} imatinib ≥1,000 ng/mL had a 2.564 times greater chance of

Table 1: Basic characteristic of chronic phase-CML patients treated with imatinib or nilotinib.

Patient's characteristic		Imatinib			Nilotinib		
		Total patient (n=23)			Total patient (n=11)		
		n	%	$\bar{x} \pm SD$	n	%	$\bar{x} \pm SD$
Sex	Man	11	47.8	–	5	45.5	–
	Woman	12	52.2	–	6	54.5	–
Age (when CML diagnosed)	18–20 y.o	1	4.3	46.70 ± 12.60	–	–	45.45 ± 13.69
	21–30 y.o	3	13.1	Median: 45 y.o	1	9.1	Median: 46 y.o
	31–40 y.o	8	34.8		4	36.4	
	41–50 y.o	6	26.1		2	18.2	
	51–60 y.o	4	17.4		2	18.2	
	61–70 y.o	1	4.3		2	18.2	
Weight	31–40 kg	2	8.7	62.30 ± 14.61 kg	–	–	59.45 ± 7.61 kg
	41–50 kg	1	4.3		–	–	
	51–60 kg	11	47.8		7	63.6	
	61–70 kg	3	13.1		2	18.2	
	71–80 kg	3	13.1		2	18.2	
	81–90 kg	2	8.7		–	–	
	91–100 kg	0	–		–	–	
	101–110 kg	1	4.3		–	–	
Imatinib duration	1–5 years	14	60.9	4.3 ± 2.08 years	11	100	2.2 ± 0.4 years
	6–10 years	9	39.1		–	–	
(+) Allopurinol	Yes	16	69.6	–	5	45.5	–
	No	7	30.4	–	6	54.5	–

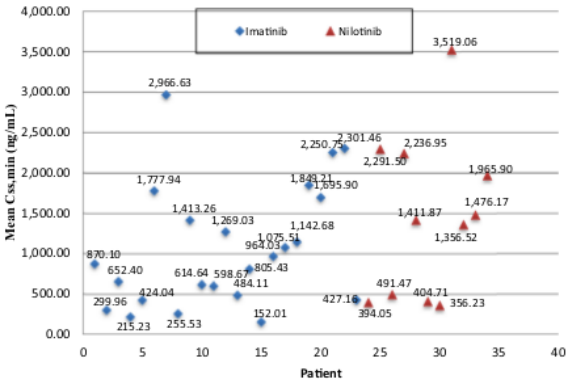

Figure 1: Distribution of imatinib and nilotinib C^{∞}_{min}.

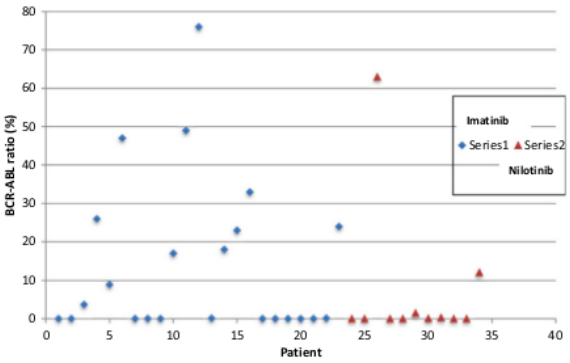

Figure 2: BCR-ABL ratio distribution from imatinib and nilotinib group.

Table 2: Imatinib and nilotinib average C^{∞}_{min}.

	Patient (n)	Average C^{∞}_{min} (ng/mL)	CV (%)
Imatinib	23	1,065.46 ± 765.71	71.87
Nilotinib	11	1445 ± 1,010.35	69.88

achieving a decrease in BCR-ABL transcripts compared to the group of patients who had C^{∞}_{min} imatinib <1,000 ng/mL (Figure 3). In contrast, there is no correlation between C^{∞}_{min} and BCR-ABL ratio in the nilotinib group.

Discussion

CML is one of the myeloproliferative disorders in hematopoietic stem cells characterized by leukocytosis (WBC level >100 × 10^9/L) and splenomegaly. About 90% of CML patients have genetic abnormalities characterized by the presence of the Philadelphia chromosome (Ph) with the fusion BCR-ABL gene. This fusion gene increases tyrosine kinase activity, which contributes to cell transformation

Table 3: Patient's clinical response with BCR-ABL ≤0.1% and BCR-ABL >0.1%.

	BCR-ABL ratio ≤ 0.1% (MMR)	BCR-ABL ratio >0.1% (non-MMR)
Imatinib		
Average Imatinib C^{∞}_{min} (ng/mL)	1,381.95	822.01
Number of patients with C^{∞}_{min} ≥1,000 ng/mL	7 (30.43%)	3 (13.04%)
Number of patients with C^{∞}_{min} <1,000 ng/mL	3 (13.04%)	10 (43.48%)
Nilotinib		
Average Nilotinib C^{∞}_{min} (ng/mL)	1,360.47	1,595.29
Number of patients with C^{∞}_{min} ≥800 ng/mL	5 (45.45%)	2 (18.18%)
Number of patients with C^{∞}_{min} <800 ng/mL	2 (18.18%)	2 (18.18%)

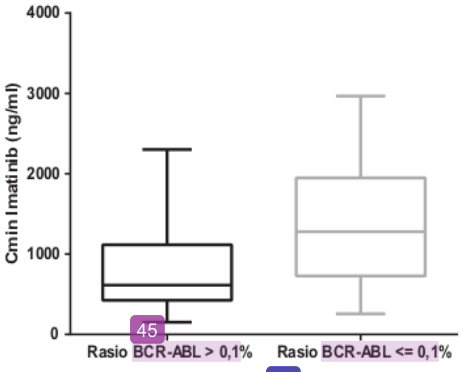

Figure 3: Imatinib C^{∞}_{min} between patients with BCR-ABL ratio >0.1% and patients with BCR-ABL ≤0.1%.

and causes uncontrolled leukemic cell growth in hematopoietic cells [14].

Imatinib and nilotinib are oral targeted-therapy of TKI groups that selectively occupy the ATP domain in ABL, which inhibits the activity of Bcr-Abl tyrosine kinase protein. Inhibition to substrate phosphorylation will inhibit the signaling pathway, which causes leukemogenesis [15]. Imatinib mesylate dosage of 400 mg/day is a standard therapy in the management of chronic phase of CML. Nilotinib has also been approved as a first-line therapy in chronic phase CML patients, clinically used in CML patients who resistant or tolerant to imatinib. By administering imatinib therapy at a dose of 400 mg/day, CML patients can reach C^{∞}_{min} target (1,000 ng/mL), a C^{∞}_{min} which can inhibit tyrosine kinase activity and therefore induce therapeutic responses. The parameter of molecular response was the ratio of BCR-ABL [16, 17]. Meanwhile, the recommended target of nilotinib C^{∞}_{min} for TDM practice, in general, is ≥800 ng/mL [18, 19].

The results of this study showed that there was high interindividual variability both in imatinib C^{∞}_{min} and nilotinib C^{∞}_{min}. This high variability was also reported in various previous studies. Data from the phase III IRIS study by Larson et al. showed a wide interindividual variability of imatinib C^{∞}_{min} that measured in steady-state, 1 h before the morning dose on 29th day in 351 patients who received a dose of imatinib 400 mg/day. In another study, wide interindividual variability of imatinib C^{∞}_{min} also obtained with the coefficient of variation of 40–60% [10, 20, 21].

Some of the factors that cause this interindividual variability include body size, age, sex, liver and renal function, interaction with other drugs which are taken together, adherence, and enzyme or transporter polymorphisms associated with PK/PD drugs [22]. In this study, there was no therapy other than imatinib/or nilotinib with/without allopurinol, which was administered together by the patient, and there were no drug interactions between them. Compliance has been monitored by interviewing before sampling to ensure there is no missing dose at least 28 days before the day of sampling.

It has been reported in various studies that imatinib has a proportional dose–response relationship. The results of correlation analysis between C^{∞}_{min} and molecular response (BCR-ABL ratio) showed that there was a correlation in the imatinib group [20].

The mean of imatinib C^{∞}_{min} in patients who achieved the BCR-ABL ratio target has been found higher than the mean of imatinib C^{∞}_{min} in patients that did not reach the target BCR-ABL ratio (1,065.46 ng/mL vs. 822.01 ng/mL). The C^{∞}_{min} ≥1,000 ng/mL was associated with an increased chance of achieving a BCR-ABL ratio of ≤0.1% (major molecular response or MMR). These results support the results of previous studies, which reported that an increase in imatinib C^{∞}_{min} correlated with a decrease in BCR-ABL transcripts characterized by a BCR-ABL ratio of ≤0.1% [20, 22]. BCR-ABL ratio ≤0.1% (MMR) can indicate a decrease in the progression toward an acceleration or blastic phase. Unlike imatinib, in the nilotinib group, there is no correlation between C^{∞}_{min} and BCR-ABL ratio even though higher C^{∞}_{min} tends to have a higher MMR level. The absence of a correlation between nilotinib exposure and the response was thought to be due to the wide interindividual variability of the nilotinib pharmacokinetic parameters. Larson also revealed that the relationship between nilotinib exposure and clinical response was not as clear as that observed in patients with imatinib. This condition may be due to nilotinib being more potent than imatinib [11]. In a

retrospective analysis of the Evaluating Nilotinib Efficacy and Safety in clinical Trials-newly diagnosed (ENESTnd) study, it was found that there was a faster decrease of BCR-ABL ratio in the nilotinib group. The 6th month of the median BCR-ABL ratio in the nilotinib group was found to be similar to the 18th month of BCR-ABL ratio in the imatinib group. There were reported to be more patients with nilotinib doses of 300 and 400 mg, which achieved a BCR-ABL ratio of <10% in the 3rd month compared to imatinib (74, 78, and 61%) [23]. The results of the Exploring Nilotinib BCR-ABL Effects (ENABL) study in the US on patients with suboptimal response to imatinib therapy showed that a decrease in the BCR-ABL ratio occurred fastest in the first 3–9 months after nilotinib use. After that, it was tended to be a plateau [24]. In the present study, the BCR-ABL ratio was observed after the use of nilotinib for more than 12 months, while the majority of patients had used nilotinib for more than 24 months and 7 (63.63%) patients had achieved a BCR-ABL ratio of ≤0.1%. Allegedly in the period of the implementation of the study, the BCR-ABL ratio has entered the plateau period so that it may cause no correlation between C^{∞}_{min} and the BCR-ABL ratio.

The distribution profile of the BCR-ABL/ABL ratio achieved by patients in the nilotinib group (Figure 2) showed that some patients experienced suboptimal responses. According to the guidelines of the European LeukemiaNet (ELN), all responses under the conditions of a major molecular response (BCR-ABL ≤0.1% IS) at the 18th month after the start of TKI therapy are considered suboptimal [25]. Reflecting on previous studies, nilotinib C^{∞}_{min} ≥800 ng/mL was associated with the achievement of the BCR-ABL ratio ≤0.1% IS in the 12th month, which indicates that nilotinib can inhibit tyrosine kinase activity well [19, 26]. This may explain that patients with nilotinib C^{∞}_{min} ≥800 ng/mL can achieve a BCR-ABL ratio of ≤0.1%. The phenomenon of having a patient with high nilotinib C^{∞}_{min}, but still unable to achieve the BCR-ABL ratio ≤0.1% was thought to be due to TKI resistance.

Leukemia cell resistance to TKI can occur due to genetic mutations in the ABL tyrosine kinase domain and changes in expression of influx/efflux transporters [27]. Patients can experience multiple mutations in the BCR-ABL gene at the same time and result in heavier resistance. More than 90 different mutations have been found in different kinase domains [28]. *In-vitro* studies result showed that nilotinib has activity against almost all cell cultures that are resistant to imatinib due to BCR-ABL mutations, except for T315I mutants [29]. In contrast to imatinib, which requires the human organic cation transporter-1 (h-OCT1) to be uptaken into leukemia cells, nilotinib activity was found to be independent from h-OCT1 [30]. In contrast, various studies have shown the role of ATP Binding Cassette Subfamily B member 1 (ABCB1) and ATP Binding Cassette Subfamily G member 2 (ABCG2) in the efflux mechanism of nilotinib from leukemia cells. In one study, it was found that the inhibition capacity of nilotinib tyrosine kinase decreased with the increasing levels of ABCB1. Therefore, ABCB1 overexpression can play a role in causing resistance to nilotinib [31–33]. Further research is needed to see mutations in the BCR-ABL gene and the expression of ABCB1 transporters in this group of patients to determine the possibility of nilotinib resistance.

Conclusion

There were high interindividual variations of imatinib and nilotinib C^{∞}_{min} in CML patients. Imatinib C^{∞}_{min} correlated with BCR-ABL ratios, but no correlation in nilotinib.

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Conflict of interest: The authors state that they have no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

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