



The Levels of FoxO3a Predict the Failure of Imatinib Mesylate Therapy among Chronic Myeloid Leukemia Patients

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Abstract

BACKGROUND: Forkhead Transcription Factor 3a (FoxO3a) has been proposed to have a high efficacy to predict the failure of imatinib mesylate (IM) therapy among chronic myeloid leukemia (CML) patients. However, the limited evidence had made this marker remained controversy.

AIM: We aimed to investigate the correlation between the levels of FoxO3a and the risk of treatment failure of IM therapy in CML patients.

METHODS: A prospective cohort study was carried out between February 2019 and February 2020 in Saiful Anwar Hospital, Malang, Indonesia. All CML patients, diagnosed using standard criteria, treated with IM 400 mg/day on our hospital during the study period were included in the study. The levels of FoxO3a were determined using the Enzyme-linked immunosorbent assay using Cusabio Biotech Kit (Cusabio Biotech Co., New York, USA). The treatment response was assessed using the European Leukemia criteria. The correlation and effect estimate between the levels of FoxO3a and treatment response of CML patients was assessed using multiple logistic regressions.

RESULTS: Fifty-three CML patients receiving IM in our hospital were included in the study, consisting of 29 patients with good response and 24 patients with non-response. Our study found that CML patients with lower levels of FoxO3a were associated with increased risk to develop treatment failure when treated with IM. Moreover, we also found that higher risk of treatment failure of IM therapy was also found in patients with increased levels of thrombocytes, basophils, and leukocytes, and lower levels of hemoglobin.

CONCLUSION: We reveal that FoxO3a is the prominent marker to predict the treatment response of CML patients treated with IM.

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Introduction

Chronic myeloid leukemia (CML), a clonal myeloproliferative disorder of hematopoietic stem cells, is the major hematological health problem [1]. The incidence of this disease was reported between 0.7 and 1.0 per 100,000 population [2]. Of them, the mortality was <15% [3]. The standard guideline for the management of CML has been established. In the guideline, tyrosine kinase inhibitors (TKIs) are used for treating patients with CML, and among all TKIs, imatinib mesylate (IM) is the most often used and approved by the US Food and Drug Administration (FDA) for the frontline therapy of CML patients [4]. The evidence revealed that, since IM therapy was introduced, the survival rate of CML patients increased to approximately 87% [3]. Briefly, imatinib binds to the BCR-ABL protein tyrosine kinase (the inactive conformation), and thereafter may prevent the conformational switching of BCR-ABL protein by

blocking the ATP binding site [5]. However, IM therapy was accompanied by numerous challenges. One of them was treatment failure [1]. The case of imatinib resistance has been reported, and the heterogeneous mechanism is proposed to underlie this resistance including BCR-ABL gene amplification and gene mutation which may lead to incomplete inhibition [6]. Previous studies had proposed some markers that might predict the treatment response of IM therapy including human organic cation transporter 1, patched homolog 1, prostaglandin-endoperoxide synthase 1, cyclooxygenase 1, and forkhead transcription factor 3a (FOXO3a) [7], [8], [9]. Of those, the role of FoxO3a had limited evidence.

FOXO3a belongs to the FOXO subfamily of forkhead transcription factors. In human, the FOXO transcription factors are encoded by five genes, including FOXO1, FOXO3a, FOXO3b, FOXO4, and FOXO6 [10]. In the context of cancer, the physiological function of FoxO3a is to stimulate some cellular mechanism including

proliferation, apoptosis, DNA damage, the activation of reactive oxygen species, cell cycle progression, and tumorigenesis [11], [12]. Several studies had proposed that FoxO3a might provide a high accuracy to predict the treatment response of IM therapy in CML patients [13], [14]. However, the lack evidence of real world study regarding the role of FoxO3a in predicting the treatment response of CML therapy has made the precise role of this marker remains controversy. Moreover, in Indonesia, no study reported the role of FoxO3a in predicting the treatment response of IM therapy. Therefore, our current study aimed to investigate the potential role of FoxO3a to estimate the treatment failure of IM therapy among CML patients. The findings of our current study might serve as the initial evaluation for treatment response of IM therapy, and thereafter treatment failure of IM therapy might be anticipated.

Methods

Study design and patients

A prospective cohort study was carried out in Saiful Anwar General Hospital between February 2019 and February 2020. We used total sampling method to recruit the patients (a total of 26 participants in each study group were needed as the minimum sample size according to the estimation that the prevalence of CML was 10–12 per 100,000 inhabitants with a 5% margin of error and 95% confidence level) [15]. The inclusion criteria were: (1) All CML patients treated in our hospital during the study period (the diagnosis criteria were adapted from previous study) [16], (2) CML patients treated with standard IM 400mg/day for at least 6 months [17], (3) aged more than 18 years old, and (4) providing the written informed consent to participate in the study. The exclusion criteria were (1) patients treated with other TKI medications, (2) patients with drugs consumption that may reduce the efficacy of IM such as prazosin, proton pump inhibitors, and erythromycin, and (3) patients suffering from diseases that may associate with increased levels of FoxO3a such as chronic obstructive pulmonary disease (COPD), vitiligo, prostate cancer, thyroid, breast, and gynecological cancer. This study had been approved by the local (Universitas Brawijaya) Ethical Committee (No. 400/098 / k.3 / 302/2019) and had been conducted following the code of ethics of Helsinki declaration.

Outcome measures

The predictor covariate in our study was the levels of FoxO3a. The levels of FoxO3a were measured by the Enzyme-linked immunosorbent assay using Cusabio Biotech Kit (Cusabio Biotech Co., New York, USA) following the manufacture instruction as described

by the previous study [18], [19]. The levels of FoxO3a were measured in picogram/milliliter (pg/mL) units. On the other hands, the outcome measures were the treatment response of IM therapy assessed using the European Leukemia Net milestone 2020 criteria [20]. Patients were defined failure response if the Bcr-Abl was more than 10%, measured using the real-time polymerase chain reaction after 6 months of IM therapy, or after 3 months of IM therapy and reconfirmed within 3 months (6 months). Moreover, we also assessed the complete blood count, measured using XS – 800i Hematology Analyzer (Sysmex Europe GmbH, Norderstedt, Germany).

Statistical analysis

The correlation between treatment response of IM therapy and their predictors was assessed using multiple logistic regressions. $p < 0.05$ indicated the significant association. We used Statistical Package for the Social Sciences 17.0 software (SPSS Inc., Chicago, IL) to analyze the data [21].

Results

Patients characteristics

A total of 53 CML patients treated with IM were analyzed. Of them, a total of 29 (55%) patients successfully achieved treatment response and 24 (45%) subjects did not achieve treatment response. Initially, we evaluated a total of 61 CML patients treated with IM. However, we excluded a total of eight patients due to having the history of drugs consumption that may reduce the effectiveness of IM (proton pump inhibitors) and suffering from diseases that are known to associate with increased levels of FoxO3a (COPD). Our study participants between two groups were age and sex matched (Table 1).

Table 1: Baseline characteristics of patients included in our study

Characteristics	Non-achieved (24)	Achieved (n=29)	p
Age (years)	43.67 ± 13.90	43.03 ± 11.43	0.780
Male	12 (50.0)	15 (51.7)	0.901
Clinical phase			
Chronic phase	8 (33.3)	23 (79.3)	0.001
Advanced phase	16 (66.7)	6 (20.7)	0.001
SOKAL risk score			
Intermediate risk	5 (20.8)	11 (37.9)	0.182
High risk	19 (79.2)	18 (62.1)	0.182
EUTOS risk score			
Low risk	16 (66.7)	29 (100.0)	0.022
High risk	8 (33.3)	0 (0.0)	0.022
Duration of therapy (months)	6.90 ± 0.88	6.98 ± 1.20	0.727
Combination with hydroxyurea	2 (14.3)	0 (0.0)	0.232

Data were presented in n (%) or mean ± SD.

Main findings

Our results identified that the levels of thrombocytes, hemoglobin, basophils, leukocytes,

CD26+, and FoxO3a contributed to treatment response of CML patients treated with IM. We found that patients with elevated levels of thrombocytes, basophils, and leukocytes were significantly found in non-response group compared to response group. Moreover, our findings also revealed that lower levels of hemoglobin and FoxO3a were correlated with increased risk of failure response of CML patients treated with IM (Table 2).

Table 2: Laboratory parameters and the levels of FoxO3a among chronic myeloid leukemia patients

Parameters	Non-achieved	Achieved	OR	95%CI	p
Hemoglobin (gr/dl)	10.43 ± 3.28	12.61 ± 1.84	0.23	0.09–0.65	0.005
Leukocytes (cells/ul)	91580 ± 141888	6849 ± 2652	5.02	1.79–14.02	0.002
Thrombocytes (cells/ul)	303125 ± 238699	191103 ± 112808	3.08	1.13–8.40	0.028
Basophils (abs)	1.20 ± 1.61	0.00 ± 0.25	7.33	2.56–20.99	0.001
Blast cells (abs)	9.21 ± 12.83	6.00 ± 7.66	1.76	0.65–4.71	0.264
BCR-ABL	28.09 ± 16.64	747.78 ± 40.16	0.65	0.24–1.73	0.383
FoxO3a (pg/mL)	42.12 ± 41.21	80.79 ± 50.50	0.22	0.08–0.61	0.004

Data were presented in mean ± SD.

Discussion

Our study found that the levels of FoxO3a were the significant predictor for assessing the treatment response of IM therapy among CML patients. We found that lower levels of FoxO3a were associated with the failure of IM therapy in CML patients. Our current findings were consistent with the reports of previous studies [22]. They also found that FoxO3a was the important predictors of treatment failure among CML patients treated with IM. The potential role of FoxO3a for predicting the treatment response had been widely proposed [11], [13]. Theoretically, it has been known that FoxO3a plays a crucial role in the pathogenesis of CML. Through the phosphatidylinositol 3-OH kinase/AKT pathway, FoxO3a may establish the phosphorylation by p210BCR-ABL tyrosine kinase, and may contribute to the proliferative of leukemic progenitors [23]. On the other hand, the inhibition of IM may interrupt the cell cycle progression and apoptosis of CML cells, and thereafter may restore the function of FoxO3a [24]. Moreover, the inhibition of Bcr-Abl kinase by IM causes the activation of FoxO3a that may further induce Bim expression through FoxO3a binding site, and therefore increases the apoptosis [24]. Another study also confirmed that FoxO3a not only induced apoptosis of leukemic stem cells but also induced arrest of the cell cycle [25]. Therefore, the lower levels of FoxO3a might play a prominent role to predict the treatment response among CML patients treated with IM as reported in our study.

Our findings also clarified that CML patients with increased levels of thrombocytes, basophils, and leukocytes and the lower levels of hemoglobin had a higher risk to develop treatment failure after treated with IM. Our results were in line with the report of previous studies. The altered levels of thrombocytes, basophils, leukocytes, and hemoglobin were also reported to affect the treatment response of IM therapy. A study revealed

that, in the 1 year of treatment response among CML patients treated with IM, patients with non-response of IM therapy had the higher levels of leukocyte compared to response group. Furthermore, they also revealed that the levels of leukocyte prior the treatment was associated with the prognosis of CML patients, suggesting that leukocyte may play a crucial role to govern the treatment of CML patients [26]. On the other hand, the lower levels of thrombocyte in response group compared to non-response group in our present study were also supported by the previous studies. They also found that higher levels of thrombocyte were found to associate with non-response of CML patients treated with IM [27], [28]. Furthermore, the previous study also supported our findings that the levels of basophils also governed the treatment response of CML patients treated with IM. They revealed that basophils might produce the autocrine growth factor for myeloid, and therefore, might attribute to the treatment response of CML patients [29], [30]. Moreover, lower levels of hemoglobin in our present study were associated with increased risk of treatment failure on CML patients treated with IM. The previous studies had also supported our findings. They found that anemic patients who received IM therapy were associated with lower rate of cytogenetic remission and shorter progression free survival [31], [32].

Our present study was the first report concerning the role of FoxO3a on predicting the treatment response of CML patients treated with IM in Indonesia. Our current finding might serve as the baseline evaluation to predict the treatment response of IM therapy. In the near future, our current findings might contribute to the improvement of IM therapy procedure in CML patients, and therefore, treatment failure of IM therapy for the management of CML patients could be prevented.

In our present study, several limitations should be discussed. First, several factors that might contribute to the severity and treatment response of CML patients treated with IM including the adherence of medication, smoking, physical activity, and dietary factors were not analyzed [33]. Second, the small sample size in our present study might drive to the false positive findings, and therefore, our findings should be interpreted with caution. Third, the short-term period of follow-up in our present study might not adequate to elucidate the real association.

Conclusion

Our study clarifies that the levels FoxO3a and hematological parameters including the levels of thrombocytes, basophils, leukocytes, and hemoglobins are the predictors of treatment failure of CML patients treated with IM. These parameters, in the near future, might be used as the initial evaluation of IM therapy for the management of CML patients.

Declarations

Ethics approval and consent to participate

Participants had provided written informed consent prior to involve in the study. Our study had been approved by local ethical committee (No. 400/098 / k.3 / 302/2019).

Availability of data and materials

Data used in our study were presented in the main text.

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Authors Contributions

Idea/concept: SOW. Design: SOW and JKF. Control/supervision: SOW, HS, PR, and YY. Data collection/processing: SOW and JKF. Extraction/Analysis/interpretation: SOW and JKF. Literature review: SOW and JKF. Writing the article: SOW and JKF. Critical review: SOW, HS, PR, and YY. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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