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Correlation between Hasford Score with Early Molecular Response in Patients with Chronic Myeloid Leukemia in Chronic Phase Treated with Imatinib

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The aim of the study is to to determine correlation Hasford score and early molecular response in chronic phase BCR-ABL-Positive CML patients treated with imatinib. This is an longitudinal observational study in newly diagnosed patients of CML chronic phase BCR-ABL-Positive treated imatinib from Januari 2017 to September 2017. Patients were stratified according to Hasford score at diagnosis. Q-PCR(Quantitative RT-PCR) were used to monitor BCR-ABL transcription levels after 3 months of imatinib treatment. Correlation between Hasford score with early molecular response were analyzed using Koefisien Kontingensi's correlation test. Results: Thirty five patients were enrolled in this study consist of 13 male and 22 female. After 3 months of imatinib treatment, EMR were 5 patients (83.3%), 11 patients (61.1%) and 2 patients (18.2%) in low, intermediate, and high risk group patients, respectively. Koefisien kontigensi test showed that there was significant correlation between Hasford score and EMR (p=0.018; r=0.431). The Hasford score correlated to early molecular response in chronic phase BCR-ABL-positive CML patients received imatinib.

Keywords: Hasford score, early molecular response, imatinib, chronic phase BCR-ABL-positive CML.

Chronic myeloid leukemia (CML) is a myeloproliferative disease characterized with leukocytosis and splenomegaly, specified with the existence of Philadelphia chromosome (Ph) or BCR-ABL Gene fusion, Ph chromosome was the reciprocal translocation t(9;22)(q34;q11) result, which combined the oncogene c-abl (ABL) long arm of chromosome 9 with breakpoint cluster region of long arm of chromosome 22. The resulting mRNA molecule coded by BCR_ABL gene formed a constitutive tyrosine kinase that caused extracellular transformation that lay the foundation for the appearance of CML.[1,2]

Its incidence in the world were considered low between 10-15 cases in 1,000,000 people each year, with more male than female (ratio of male: female = 1.4:1) and often happened at the age of 40-60 years old. In western population, the median of patients' age when diagnosed was 55-65 years old. In Asia, Africa, Southern/Eastern Europe and Latin America the median of patients' age was ranging from 38 to 41 years old.[3] Based on an epidemiological study in Indonesia in 2009-2011, the median age at the time of diagnosis were 34-35 years old (average 36 years old).[4]

Use of tyrosine kinase inhibitor (TKI) has affected the survival rate of newly CML

chronic phase patients to become almost the same with normal individual. Currently the works are being focused to discover how is the long term outcome of CML patients can be predicted. Low-intermediate Hasford score were being identified as a risk factor of reaching higher early molecular and cytogenetic response compared to high Hasford score.[5]

Hasford score which was developed in 1988, were used to know the risk of CML patient's progressivity. Hasford score used as prognotic factor in the pre TKI era (busulfan, interferon), but known to be beneficial as a predicting of TKI therapy response. Currently several researcher used Hasford score to predict therapy response in CML chronic phase patients that received imatinib. It was reported that no scoring system could predict the molecular response, but in the research conducted by Dybko *et al*., (2016) in Poland toward 88 newly diagnosed of CML chronic phase patients that received Imatinib, it was reported that Hasford score were beneficial in predicting the molecular response in CML chronic phase patients.[6] Research by Banjar and Alshobi, 2017 reported that Hasford score exceeded other score in predicting the major molecular response corresponded with risk factor identification, with 63% accuracy.[7] Research by Kuntegowdanahalli *et al*., (2016) reported that Hasford score had a complete cytogenetic, and major molecular response prediction, this showed the same result as a research by Yamamoto *et al*., (2014).[8,9] Hasford score using 6 parameters measured in diagnosis consisted of patient's age, lien size, thrombocyte count, presentation of blast, eosinophil and basophil. This score used eosinophilic and basophilic parameters in score calculation compared to Sokal score. Eosinophilic and basophilic parameter hold a crucial role in the progressivity and prognosis of CML.[10,11,12]. Hasford score classify CML patients into 3 risk groups: low, intermediate, and high risk. [13]

Therapy response a very important matter after the administration of a therapy. There are 3 therapy response criteria to evaluate the result of TKI therapy, which were hematological, cytogenetic, and molecular response. In this research evaluation toward early molecular response with quantitative PCR were conducted. Early molecular response (EMR) was recommended by NCCN in 2019 as an early molecular response evaluation. EMR was defined as the BCR-ABL transcript rate <10% International Scale (IS) in 3 months.[5,14,15] Research by Chikkodi *et al*., in 124 newly diagnosed of CML chronic phase patients that received imatinib, 82.3% patient reached EMR, low-intermediate Hasford score had a higher prediction to reach EMR (p=0,0179). CML chronic phase patient that experience EMR had a better later therapy response.[5] EMR were linked with the increased probability in achieving major molecular response (MMR) and molecular response in ($MR^{4,5}$).[16] Failure of achieving EMR were linked with the low molecular response rate, increased progressivity risk and low survival compared with those who achieved EMR.[1]

MATERIALS AND METHODS

This research was an analytical prospective longitudinal study. This research was conducted at hematology clinic, Internal Medicine Department, Dr Soetomo Hospital, Surabaya starting from January of 2017. The kind of data used were primary data directly collected by researcher trough interview, physical examination, and blood sample collection. The diagnosis of CML was based on characteristic peripheral blood smear and was confirmed by detection of BCR/ABL translocation by PCR. The patients were newly diagnosed of CML BCR-ABL positive chronic phase that have never received imatinib. Patients aged more than 18 years, have a >60% Karnofsky appearance status, and BCR-ABL transcript rate of above 10% (IS) were included. Meanwhile patients that were pregnant, infected or inflamed, cirrhosis hepatis or malaria, in the usage of drugs affecting leucocyte count or imatinib level, with other myeloproliferative diseases (PV, TE, MMM) were excluded. Drop out were patients that were deceased, withdrew from the research, experience decreased dosage of imatinib, progression toward acceleration phase or blast crisis, serious adverse event,. To determine the correlation between Hasford score and early molecular response, Contingency Coefficient statistical test result was used. The interpretation of correlation test were based on p-value. The condition used were: an correlation status can be stated as significance if the p-value acquired were smaller than the significant value of 5% (>5%).

RESULTS

This research were participated by 41 newly diagnosed of CML chronic phase BCR-ABL patients that visited Soetomo Hospital Surabaya, which fulfill the inclusion and exclusion criteria only 35 patients, since 3 patients were deceased because of sepsis, 2 patient withdrew from the research because of a work related reason in Kalimantan and Madura, and 1 patient progressed toward acceleration phase. Clinical characteristics of CML BCR-ABL positive chronic phase patients that received imatinib (table 1).

The scale of prognostic factor of CML chronic phase BCR-ABL positive patients that received imatinib treatment were determined using Hasford formula. Hasford score was based on the algorithm that consisted of the following parameters which were measured in diagnosis: patient's age, spleen size, thrombocyte count, presentation of eosinophil, basophil, and circulatory presentation of blast. This score differentiate patients into three groups: low, intermediate, and high (table 2).

In this study, diagnosis of CML was confirmed by quantitative PCR examination (qPCR). Early molecular response (BCR-ABL transcript rate of <10 %(IS)) CML chronic phase BCR-ABL patients were determined by measuring the BCR-ABL transcript rate after 3 months of imatinib therapy (table 3). There were 33 patients who experienced decline in transcript rate of BCR-ABL and there was 1 patient with high Hasford score (no.2 sample) and 1 patient with intermediate Hasford score (No. 19 sample) who experienced uplifting in BCR-ABL transcript rate after 3 months of imatinib treatment. (figure 1)

Statistical test of the difference in change of BCR-ABL transcript rate between the Hasford score groups ware analyzed with Kruskal-Wallis

Table 1. Characteristic of 35 patients with CML at diagnosis

Characteristic		Result
Sex	Male	13 (37.1%)
	Female	22 (62.9%)
Age (year)	Median (min-max)	41 (18-63)
Hemoglobin (g/dL)	Average ± SD	9.41± 1.6
Leucocyte (/µL)	Median (min-max)	212,840 (10,300 – 678,000)
Thrombocyte (/µL)	Average ± SD	590,400 ± 290,371
Eosinophil (%)	Median (min-max)	2.9 (0 -19.2)
Basophil (%)	Median (min-max)	3.14(0 – 15.5)
Blas (%)	Median (min-max)	3.7 (0 - 10)
BCR-ABL transcript rate (IS)(%)	Average ± SD	43.18 ± 21.33
Spleen size (cm)	Average ± SD	16.2 ± 8.5
Hasford	Low	6 (17.1%)
	Intermediate	18 (51.4%)
	High	11 (31.4%)

Table 2. Hasford score distribution at diagnosis

No	Hasford Score	Frequency	%
1	Low (≤ 780)	6	17.1
2	Intermediate (>780-≤1480)	18	51.4
3	High (>1480)	11	31.4

Table 3. Early Molecular Response Distribution

No	Early Molecular Response	Frequency	%
1	Yes (*BCR-ABL*<10%)	18	51.4
2	No (*BCR-ABL*ed10%)	17	48.6

Table 4. Contingency Coefficient analysis result of Hasford score and Early Molecular Response

	Early Molecular Response		Correlation
	p	r	
Hasford Score	0.018	0.431	Significance

test. Statistically, there was a significant difference between the difference in change of BCR-ABL transcript rate between the Hasford score groups (p=0.006). To determine which group had a difference, then post hoc analysis were conducted. Post hoc analysis test for Kruskal Wallis test was Mann-Whitney test. Mann-Whitney test were conducted between the low and intermediate Hasford score, low and high Hasford score and also intermediate and high Hasford score. With Mann-Whitney test the following result were acquired:

a. Low and intermediate Hasford score group acquired p=0.005

b. Low and high Hasford Score group acquired p=0.002

c. Intermediate and high Hasford group acquired p=0.787

It was concluded that there was a difference in change of BCR-ABL transcript rate between the low, intermediate, and high Hasford score groups, meanwhile between the intermediate and high Hasford score groups there was no difference in change of BCR-ABL transcript rate. It was determined that as the Hasford score risen, the lower the early molecular response (EMR) and vice versa (figure 2).

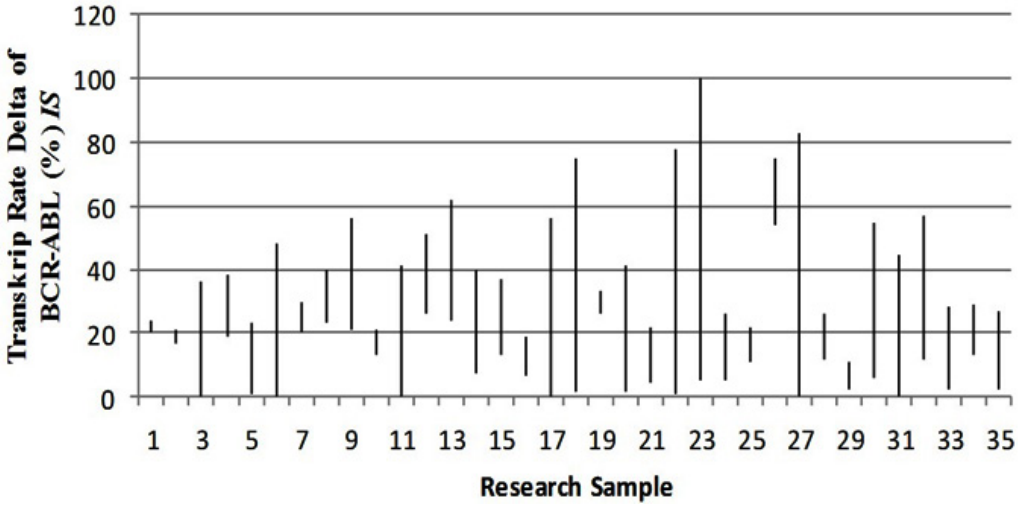

Fig.1. The difference in change BCR-ABL transcript rate before and after 3 months imatinib therapy

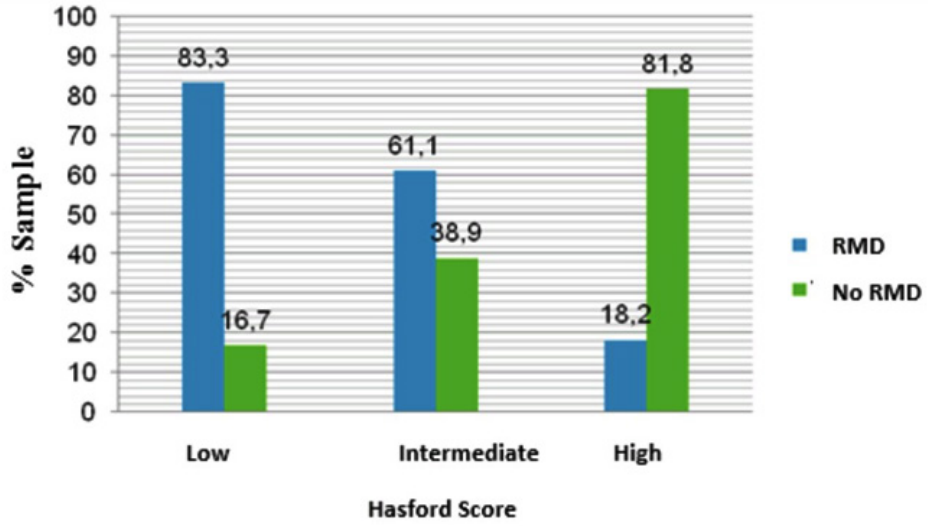

Fig. 2. Hasford score with early Molecular Response

The correlation analysis result between Hasford score with early molecular response using Contingency Coefficient correlation test acquired p=0.018; r=0.413. From those result, p=0.018 was acquired which showed that the correlation between Hasford score and early molecular response (table 4).

DISCUSSION

There were 17.1% of low, 51.4% intermediate, and 31.4% high Hasford score, this was different with the research conducted by Chikkodi *et al*., where there were 29.8% low, 55% intermediate, and 15.3% high Hasford score, also with the research by Kuntegowdanahalli *et al*., where there were 20.2% low, 62.3% intermediate and 17.5% high Hasford score in their subject patients, and also with the research by Elbedewy *et al*., where there were 38.9% low, 49.1% intermediate and 12% high Hasford score in their subject patients.[5,8,17]

The most of the patient provided an early molecular response (EMR) of 51.4% meanwhile the 48.6% others didn't provided a response. There were 4 patients that reached a complete molecular response (no detection of BCR-ABL rate), and 2 patient that reached major molecular response (BCR-ABL expression of d"1% (IS)). This research had a different result with the research conducted by Hafstein *et al*., where they acquired a result of 74.2% of patients reached EMR and 27.6% didn't reached EMR, statistically significant (p<0.001).[18]

In this study, there were 33 patients who experienced a decline in their BCR-ABL transcript rate and there were 2 patient that experienced an increase of BCR-ABL transcript rate after 3 months of imatinib therapy (1 patient with high Hasford score and 1 patient with intermediate Hasford score). The increase of BCR-ABL transcript rate was probably caused by mutation, cytogenetic variation or additional chromosome abnormalities.

Statistical analysis on the difference in change of BCR-ABL transcript rate between the Hasford score groups were analyzed using Kruskal-Wallis test (p=0.006). The post hoc analysis test for Kruskal-Wallis was Mann-Whitney. There were difference in change of BCR-ABL transcript rate between the low and intermediate Hasford score (p=0.005) also between low and high Hasford score groups (p=0.002), meanwhile between the intermediate and high Hasford score groups there were no difference in change of BCR-ABL transcript rate (p=0.787). This result was different with the research conducted by Asharianti & Ugroseno, 2013 which reported there was no difference in change of the BCR-ABL transcript rate between the Sokal score groups (p=0.734).[19] Banford *et al*., reported that in patients that didn't reached EMR in 3 months, the BCR-ABL transcript rate can become the differentiation in determining bad prognosis in the later stage. Patients with BCR-ABL halving time <76 days had significantly superior outcome compared with patients whose BCR-ABL value did not halve by 72 days.[20]

Hasford score corelation analysis result with early molecular response by using Contingency Coefficient acquired a significant correlation with p=0.018; r=0.431 (table 4). This research had almost the same result with the research by Chikkodi *et al*., which showed a significant correlation between Hasford score and early molecular response (p=0.0179). Patient with low Hasford score had the highest proportion of early molecular response (83.3%) followed by intermediate score (61.1%), and high score (18.2%). This showed that patient with lower Hasford score had higher early molecular response and vice versa. Low-intermediate Hasford score were identified as a risk factor in reaching higher EMR compared to high Hasford score.[5]

CONCLUSION

The conclusion of the study that the Hasford score correlated to early molecular response in CML chronic phase BCR-ABL positive patients that received imatinib.

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