Original Article

Evaluation of Treatment Outcomes of Patients with Chronic Phase Chronic Myelogenous Leukemia (CML) to Imatinib: A Single Centre Experience 2010-2015 Period

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Abstract

Background: Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm that accounts for approximately 15% of newly diagnosed cases of leukemia in adults. The incidence of CML has increased two-fold from 1241 to 2517 cases from 1970 -2017. Tyrosine kinase inhibitor, such as Imatinib, is the first-line treatment of chronic phase CML that efficiently inhibits the BCR–ABL1 kinase. Treatment response can be evaluated by measuring the Complete Hematologic Response (CHR) and Major Molecular Response (MMR). We aim to evaluate the treatment outcomes of chronic phase CML patients to Imatinib and their characteristics. **Materials and Methods:** We collected data retrospectively from medical records of newly diagnosed chronic phase CML patients from 2010 to 2015 period at Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, regarding age, gender, symptoms, splenomegaly, complete blood count, BCR-ABL variant transcript, Sokal and ELTS scores, last treatment, Complete Hematological Response (CHR), Major Molecular Response (MMR), and their last phase. Association between patient characteristics and treatment response was evaluated. **Results:** Out of 60 patients with CML, the median age was 43 years (24-72), including 36 (60%) men and 24 (40%) women. There were 46 (76.7%) patients with symptoms and 14 (23.3%) patients without symptoms. Splenomegaly was found in 42 (70%) patients. BCR-ABL transcript variant of b2a2 was the most frequent (51.7% of patients). Intermediate-high risk patients outnumber low-risk patients. CHR was found in 44 (74.6%) patients while MMR was found in 16 (33.3%) patients. There were 51 (85%) patients who remained in the chronic phase while 9 (15%) patients progressed to the accelerated phase. CHR was significantly different between low and intermediate-high risk Sokal score group (p=0.025) and MMR was significantly different between leukocytosis more than 100.000/µL, vs leukocytosis less than 100.000/µL (p=0.001) and low vs intermediate-high risk ELTS score group (p=0.038. **Conclusion:** The median age of our chronic phase CML patients was similar to the other Asian countries. We had poorer treatment response which might be related to a high number of intermediate-high risk patients and delays in diagnosis.

Keywords: chronic phase, chronic myeloid leukemia, imatinib, treatment response

Introduction

According to 2016 classification of world health organization (WHO), chronic myelogenous leukemia (CML) is a part of myeloproliferative neoplasm which is a group of diseases characterized by over-proliferation in a certain hematopoietic cycle.[1,2] The incidence of CML is 15% of all adult hematologic neoplasm with more propensity in males than females.[3] In Southeast Asia, from 1997-2017, the incidence of CML increases

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two-fold from 1241 to 2517 cases. Asian countries have a younger median of age at CML diagnosis as compared to western countries. In the United States, the median age at CML diagnosis is 65 years.[4] Meanwhile, in India, the median age at CML diagnosis varied in population from 32 years to 42 years.[5]

CML is caused by a reciprocal translocation between ABL segment in chromosome 9 and breakpoint cluster region (BCR) segment in chromosome 22 [t(9;22)(q34;q11)] which produces the Philadelphia chromosome and BCR-ABL. BCR-ABL gene generates BCR-ABL transcript and tyrosine kinase-rich protein which has a role in cell growth.[6,7] In CML, generally, BCR-ABL transcript variants are e13a2 (b2a2), e14a2 (b3a2), or both, but in some cases e1a2 is found.[8,9] The classic fusions are b2a2 or b3a2, fusing exon 13 (b2) or exon 14 (b3) of BCR, respectively, to exon 2 (a2) of ABL. Both b3a2 and b2a2 transcripts can be formed as a result of alternative splicing. These transcripts lead to the production of an 8.5 kb transcript coding for a 210-kDa (p210) chimeric protein, leading to enhanced tyrosine kinase activity and activation of leukemogenic pathways.[10]

Imatinib mesylate was the first Tyrosine Kinase Inhibitor (TKI) to receive approval for the treatment of patients with chronic phase CML. It acts via competitive inhibition at the adenosine triphosphate (ATP)-binding site of the BCR–ABL oncoprotein, which results in the inhibition of phosphorylation of proteins involved in cell signal transduction. It efficiently inhibits the BCR–ABL1 kinase, but, among others, also blocks the platelet derived growth factor (PDGF) receptors and the tyrosine kinase.[11] The goal of CML treatments are the return of normal blood counts, reduction and elimination of the Ph chromosome, and the reduction and elimination of BCR-ABL1 gene expression. Progression toward these goals can be determined by the measurement of hematologic and molecular responses. CHR is achieved when laboratory values return to normal levels, with leucocyte count <10.000/mm, platelet count <450.000 mm, the presence of <5% myelocytes plus metamyelocytes, the presence of <20% basophils, the absence of blasts and promyelocytes in peripheral blood, and the absence of extramedullary involvement.[12] An MMR is achieved when the level of BCR-ABL transcript $\leq$ 0.1% on the International Scale from standardized baseline after more than 12 months treatment with Imatinib. MMR was assessed by BCR-ABL with Polymerase Chain Reaction (PCR) method.[13]

A previous study in multi-center in Indonesia evaluating the demographic, clinical, and hematologic characteristics of CML patients had been conducted in the 2010-2011 period.[3] However, the population of the study included not only chronic phase patients but also accelerated and blast phase patients. In this study, we will focus on chronic phase CML patients at the time of diagnosis in a different period.

Materials and Methods

We derived data from medical records of newly diagnosed CML patients in 2010-2015 at Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia. This study has been approved by the Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo National General Hospital committee of the health research ethics. We collected data regarding age, gender, symptoms, splenomegaly, complete blood count (CBC), BCR-ABL variant transcript, last medicine administered (Imatinib or Nilotinib), Complete Hematologic Response (CHR), Major Molecular Response (MMR), and last phase of CML of the patients. Risk stratification using Sokal and EUTOS Long Term Survival (ELTS) scores was also assessed from the data above. Inclusion criteria of the study included subjects above 18 years old and underwent qualitative BCR-ABL examination. Exclusion criteria of the study were patients with incomplete or lost medical records.

Patient's characteristics were analyzed descriptively and summarized in frequency tables. We also analyzed the association between characteristics of the patients and treatment response (CHR and MMR) using x^2-test in IBM SPSS ver.20 for Windows. Statistically significant result was considered as $p < 0.005$.

Results

There were 60 patients diagnosed with CML who fulfilled the criteria in the study. Characteristics of the patients at the time of diagnosis can be seen in Table 1. The median age of patients was 43 years. The ratio of males to females was 1.5:1. Half of the population has b2a2 transcript and an uncommon transcript found in the population was e1a2. The number of patients who had Hb <10 g/dL was comparable with those who had Hb ≥10 g/dL. Leukocytosis of more than 100.000/µL was found in 70% of patients and thrombocytosis was found in 41.7% of patients. The complete blood count profile is summarized in Table 2.

Table 1: Patients' Characteristics at Diagnosis

Characteristic	Result
Age (Year)	
Mean	45 (SD ±12.037)
Median	43
Range	24-72
Gender	
Male	36 (60%)
Female	24 (40%)
Symptoms at diagnosis	
With symptoms	46 (76.7%)

No symptoms	14 (23.3%)
Splenomegaly (Schuffner)	
None	18 (30%)
S I-S IV	29 (48.3%)
S V-S VIII	13 (21.7%)
BCR-ABL Transcript	
b3a2	26 (43.3%)
b2a2	31 (51.7%)
b3a2 and b2a2	2 (3.3%)
e1a2	1 (1.7%)

Table 2: Complete Blood Count Profile

Variable	Result
Hemoglobin (g/dL)	
Mean	10.5 (SD ±2.546)
Range	4.06-16.7
<10 g/dL	26 (43.3%)
≥10 g/dL	34 (56.7%)
Leukocyte (x103/µL)	
Leukocytosis (>100.000)	42 (70%)
Mean	203.975 (SD ±151,855)
Range	5-604.3
Thrombocyte	
Thrombocytosis (> 450.000)	25 (41.7%)
Mean	516,467 (SD ± 326,286)
Range	96,000-1,824,000
Basophil (%)	
Median	2.7
Range	0-29
Eosinophil (%)	
Median	2.8
Range	0-47
Neutrophil (%)	
Bands	
Median	0.0
Range	0-34
Segmented	
Median	58.0
Range	0-94
Lymphocyte (%)	
Median	6,0
Range	0-58.1
Monocyte (%)	
Median	2.0
Range	0-13,7
Blast (%)	
Presence	46 (86.8%)
Median	3.0
Range	0-13
Promyelocyte (%)	
Presence	40 (95.2%)
Median	5.0
Range	0-40
Metamyelocyte (%)	
Presence	43 (100%)
Median	6.0
Range	1-32
Myelocyte (%)	
Presence	43 (97.7%)
Median	8.5
Range	0-28

In the result of risk stratification of CML patients based on Sokal and ELTS score, the most frequent group was intermediate-risk patients. The distribution of patients according to risk groups is shown in Table 3.

Table 3: Risk Stratification of CML

Scoring	Result
Sokal score	
Low risk	12 (20%)
Intermediate risk	25 (41.7%)
High risk	23 (38.3%)
ELTS score	
Low risk	24 (40%)
Intermediate risk	30 (50%)
High risk	6 (10%)

ELTS: EUTOS Long Term Survival

In this study, the first-line of treatment was Imatinib to all patients, after follow-up, 51 patients were still treated with Imatinib, and 8 patients were shifted to Nilotinib. After three months of treatment, three-quarters of the patients had Complete Hematologic Response (CHR). However, after >12 months of treatment, the number of patients who had no Major Molecular Response (MMR) was higher than those who had MMR with a ratio of 1.93 (31:16). At the last follow-up, 50 (84.7%) patients remained in the chronic phase (84.7%), 9 (15.3%) patients progressed to the accelerated phase, and no patients ended with the blast crisis phase. The outcomes of patients after treatment with Imatinib are summarized in Table 4.

Table 4: Last therapy, treatment response, and disease progression

Variables	N=60
Last Therapy	
Imatinib	52 (86.7%)
Nilotinib	8 (13.3%)
Complete Hematologic Response (CHR)	
Yes	45 (75%)
No	15 (25%)
Major Molecular Response (MMR)	
Yes	16 (26.7%)
No	32 (53.3)
Not available	12 (20%)
Disease Progression	
Chronic	51 (85%)
Accelerated	9 (15%)
Blast Crisis	0 (0%)

We analyzed the association between patients' characteristics and treatment response (Table 5 and Table 6). We found that Sokal score was associated with CHR (p=0.025). Meanwhile, MMR was associated with leukocytosis more than 100.000/µL (p=0.001) and ELTS score (p=0.038).

Table 5: Patient's Characteristic Association with Complete Hematologic Response

Characteristics	CHR (N=45)	No CHR (N=)15	P value
Symptomatic			
Yes	35	11	0.724
No	10	4	

Splenomegaly			
Yes	13	5	0.745
No	32	10	
BCR-ABL transcript			
b2a2	25	6	0.193
b3a2	17	9	
Hemoglobin			
<10 g/dL	20	6	0.764
≥10 g/dL	25	9	
Leukocytosis (>100,000)			
Yes	34	8	0.104
No	11	7	
Thrombocytosis (>450,000)			
Yes	18	9	0.178
No	27	6	
Sokal score			
Low risk	12	0	**0.025**
Intermediate-high risk	33	15	
ELTS score			
Low risk	19	5	0.543
Intermediate-high risk	26	10	

CHR: Complete Hematologic Response, ELTS: EUTOS Long Term Survival

Table 6: Patient's Characteristic association with Major Molecular Response

Characteristics	MMR (N=16)	No MMR (N=32)	P value
Symptomatic			
Yes	11	27	0.209
No	5	5	
Splenomegaly			
Yes	6	6	0.157
No	10	26	
BCR-ABL transcript			
b2a2	9	16	0.850
b3a2	7	14	
Hemoglobin			
<10 g/dL	5	17	0.152
≥10 g/dL	11	15	
Leukocytosis (>100,000)			
Yes	7	28	**0.001**
No	9	4	
Thrombocytosis (>450,000)			
Yes	8	15	0.838
No	8	17	
Sokal score			
Low risk	5	4	0.117
Intermediate-high risk	11	28	
ELTS score			
Low risk	10	10	**0.038**
Intermediate-high risk	6	22	

MMR: Major Molecular Response, ELTS: EUTOS Long Term Survival

Discussion

In this study, we analyzed the characteristics of CML patients in a single center in Indonesia including the demographic, clinical, hematologic, and treatment response to imatinib. Out of 60 patients with CML, the median age was 43 years, and 36 (60%) were male. This result was consistent with other Asian countries that have median age a decade younger than western countries. [14,15] However, a previous multicenter study in Indonesia in 2010-2011 reported that the median age of CML was 34-35 years.[3] Male predominance in this study was consistent with most studies.[14-16] Nearly 75% of patients in our study were showing symptoms associated with splenomegaly and anemia. This result was similar to the studies in Pakistan by Bhatti et al., and in Tanzania by Nasser et al., who reported almost all the patients at the time of diagnosis were presented with symptoms. However, the number of asymptomatic patients in this study was lower as compared to European Countries.[17-19] The result also suggests that most of our patients were diagnosed rather late. The distribution of BCR-ABL transcript variants in our population revealed b2a2 transcript as the most frequent. This result was different compared to studies in other Asian Countries that reported b3a2 transcript as the most frequent in CML patients.[20,21] Pratik Deb et al., also reported that the frequency of b3a2 transcript was superior to b2a2 but it did not reveal any significant difference of treatment response in two patient populations.[22] This result was different compared with another study by Mourad Nachi et al. which reported that patients with b3a2 transcript may be associated with a better response to Imatinib therapy.[23] However, de Lemos et al., reported that b2a2 transcripts have a better molecular response than b3a2. [24]

In terms of laboratory tests, the CBC showed anemia, leukocytosis more than 100.000/µL, and thrombocytosis. These hematologic characteristics were common characteristics of CML. Nearly all of our chronic phase CML patients had leukocytosis more than 100.000/µL and only less than half of patients had thrombocytosis which is similar to the study conducted by Bhatti et al., in Northern Pakistan.[19]

Based on SOKAL and ELTS scoring systems, the number of low-risk patients was fewer than non-low risk (intermediate and high risk) patients. This was related to our patient's characteristics that mostly were symptomatic and had splenomegaly. This result was similar to the study in Pakistan and India which predominated with intermediate and high-risk patients.[25,19] Even though most of our patients were at intermediate-high risk, imatinib was still chosen as the first-line treatment. This is due to the the reason that only imatinib and nilotinib are available drugs in our country. Thereby, nilotinib was reserved as the second-line treatment for patients who respond poorly to imatinib or patients with progressive disease. Only 33.33% of patients treated with imatinib had MMR. A study in Lebanon claimed that 58% of patients treated with imatinib achieved MMR after 18 months. [16] However, our results were only slightly lower as compared to a study in the developing countries of

West Asia, which reported 38% of patients treated with Imatinib achieved MMR after >12 months follow-up.[26] The achievement of MMR predicts superior long-term clinical outcomes, namely, progression-free survival (PFS) and event-free survival. Therefore, failure to achieve an MMR after 12 months of Imatinib therapy is considered as "warning sign" that these CML patients may require more frequent monitoring.[13] The number of patients treated with imatinib who developed CHR was also lower than the randomized controlled trial (RCT) study conducted by O'Brien et al., in 2003.[27] This result might be related to the fact that our population predominated with intermediate and high risk patients. European LeukemiaNet recommendations state that the achievement of CHR within 3 months from the start of therapy is an optimal response. Any loss of CHR predicted shorter PFS and overall survival.[28] Imatinib was considered effective in our study reflected by only 15% of chronic phase CML patients who progressed to accelerated phase. This is matched with a study conducted by Zhao et al., in China which reported 78% of chronic phase CML patients treated with Imatinib had 3-year progression-free survival.[29]

We analyzed the association between baseline characteristics of the patients and treatment response (CHR and MMR). We found a significant difference between low and intermediate-high risk group patients for CHR (p=0.025). In our study, all low-risk Sokal score group patients had CHR. This result is in agreement with the findings of Usman et al., who reported that a low Sokal score at baseline predicts higher level of hematological response.[30] However, for MMR, we found that there was a significant difference between patients with leukocytosis greater than 100.000/µL and those with leukocytosis less than 100.000/µL (p=0.001). The number of patients with leukocytosis more than 100.000/µL,that had no MMR was higher than those with leukocytosis less than 100.000/µL at the time of diagnosis. This result matched with a study in Tanzania by Nasser et al., that reported patients with higher mean leukocyte count were less likely to achieve optimal response.[18] We also found a significant difference between low and intermediate-high risk ELTS score group patients for MMR (p=0.038) but no significant difference between Sokal score group (p=0.117). The number of patients in the intermediate-high risk ELTS score group who had no MMR was higher than those in the low-risk group. Our result was supported by a study carried out by Sato et al., which reported that ELTS score has the highest predictive value for treatment response (MMR by 12 months) which revealed a significant difference between high-risk and non-high-risk patients.[31] However, there was a difference in our study in which we merged the intermediate and high-risk ELTS score group.

Conclusion

In summary, the study revealed median age of our population was similar to other Asian countries which are younger than Caucasian. Treatment response was poorer compared to other studies. This might be related to a high number of intermediate and high-risk patients and delay in diagnosis.

Limitation

In this study, we could only include the patients who routinely came for a check-up while the patients who did not come and those who did not survive were not being evaluated.

Conflict of Interest

The authors have stated that there was no conflict of interests.

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