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Predictive Factors of Patients with Chronic Phase Chronic Myeloid Leukemia Treated with Tyrosine Kinase Inhibitor

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Summary

Background: Chronic Myeloid Leukemia (CML) is a hematological malignancy caused by an abnormality of the Philadelphia chromosome. Along with the development of CML treatment, the discovery of tyrosine kinase inhibitors (TKI) paved the way for CML patient and lead to longer survival rate. It is very important to know whether the treatment response is successful or not as well as the predictive factors that can improve the therapeutic response of CML patients treated with TKI.

Methods: This study is an observational cohort study conducted for 12 months long and involving 40 CML patients treated with TKI, both hematological and molecular therapy response were evaluated in this study. We analyzed some predictive factors such as relationship between early clinical and laboratory symptoms before the treatment by TKI and treatment response and the relationship between Eutos, Sokal and Hasford scores and treatment response.

Results: A total of 40 chronic phase CML patients, consist of 25 men (62.5%) and 15 women (37.5%) with mean age of 37 years. Most common clinical manifestation was weight loss (100%), followed by splenomegaly in 39 people (97.5%). Complete Hematologic Response (CHR) after 3 months of TKI therapy was achieved by 15 patients (37.5%). The number of patients who achieved 6-months CHR increased to 19 patients (47.5%). Among 37 samples who performed quantitative examination on fusion of the breakpoint cluster region (BCR) gene on chromosome 22 gene in band q11 and Abelson murine leukemia (ABL1) gene on chromosome 9 band q34 (BCR-ABL), 20 patients (54%) achieved major molecular response (MMR), and the remaining 17 (45.9%) had not yet achieved MMR. We found significant relationship between basophils and quantitative BCR-ABL levels ($p < 0.01$). We didn't find any relationships between these three scores (Eutos, Sokal and Hasford) with treatment response, both hematological and molecular treatment response.

Conclusions: The prevalence of CHR at 3 months was 37.5% meanwhile prevalence of MMR after 12 months was 54%. We found that basophil percent at 3 months after treatment is predictive factor and significantly associated with quantitative BCR-ABL levels ($p < 0.05$).

Key Words: Chronic Myeloid Leukemia, predictive factors, treatment response

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Introduction

CML is the first malignancy that has been successfully linked directly to the presence of a chromosomal abnormality known as the Philadelphia chromosome. This chromosome occurs as a result of a reciprocal translocation process between chromosomes 9 and 22 [t(9;22)]. This t(9;22) translocation resulted in head and tail fusion of the breakpoint cluster region (BCR) gene on chromosome 22 gene in band q11 and ABL1 gene on chromosome 9 band q34. The result of this BCR-ABL fusion is the formation of a protein that can dysregulate tyrosine kinase activity, resulting in leukemogenesis which is the main pathogenesis process for CML (NCCN, 2016). The incidence of CML accounts for almost 15% of all cases of leukemia in adult cases. Other data in 2003-2009 stated that the 5-year survival rate of CML patients in the USA was 58.6%. This is significantly different from 1975-1977 which was only 21%, and probably due to the discovery of TKI therapy around 2000[1].

Treatment of CML before the era of 2000 was conventional cytostatic drugs such as busulfan, hydroxyurea, interferon, chemotherapy and bone marrow transplantation in several centers. However, a few years later the treatment strategy changed with the discovery of TKI drugs that act as target therapy by suppressing the activity of tyrosine kinase so that the leukemogenesis process does not occur. Imatinib is the first-generation TKI class that was launched. Some studies even stated that TKI therapy is superior first-line therapy of chronic phase-chronic myeloid leukemia (CP-CML) compared to allogeneic bone marrow transplant therapy due to incidence of transplant-related mortality. Later on, new fact emerged that some cases were found to be insensitive to imatinib or only able to maintain the desired therapeutic response for a short time. Therefore, studies were carried out to find factors that influence resistance and the discovery of the latest generation of TKI after the imatinib era in order to improve the response to therapy for patients with CML. The result is the discovery of the second generation of TKI, such as dasatinib, nilotinib, polatinib or bosutinib. Among all types of TKI drugs, only 2 types of drugs are currently available in Indonesia, namely imatinib and nilotinib.

To date, there are few scoring system that has been established, they are Sokal, Hasford and Eutos. These scores have important role in determining prognosis of CML patients in term of treatment response or clinical outcomes related to TKI therapy. The Sokal score system was developed to predict the prognosis of CML patients with the Philadelphia chromosome (+) who were treated with imatinib and a second-generation TKI. On the other hand, Hasford scoring system was developed to predict the overall prognosis of 10-year survival of CML patients treated with Interferon alpha. Sokal and Hasford were found to be more successful in predicting the prognosis of high-risk CML patients, compared to low-risk and intermediate groups whereas Eutos score has successfully predicted the probability of achieving Complete Cytogenetic Response (CCyR) at month 18 and Progression Free Survival (PFS) for CML patients with first-line TKI imatinib[2-4].

In order to achieve an optimal response to therapy, it is very important to know early or before starting treatment whether any predictive factors such as clinical and laboratory conditions can affect the prognosis of CML patients during TKI therapy. Considering that CML is a type of malignancy that is often found in Indonesia, but not many studies have been carried out in Indonesia, especially in Bali, we conducted research regarding predictive factors and an appropriate prognostic score system that can be applied to patients with CML who were treated at the Internal Medicine Polyclinic, Sanglah Hospital, Denpasar.

Methods

Study population and sample collection

This study was an observational cohort design. All samples in this study were patients diagnosed with CML chronic phase age ≥ 18 years old with positive Philadelphia chromosome and treated with TKI regiment (imatinib, nilotinib) in Sanglah General Hospital, Bali between September 2015-September 2016. All of the patients monitored their CHR and MMR in time points defined by European Leukemia Net (ELN). CHR is defined as achieving leukocyte count < 10,000/mm^3, platelet count < 450,000/mm^3, and spleen not palpable within 3 months of therapy where MMR is defined as achieving a BCR-ABL transcript level equal to or less

than 0.1% at 12 months by RT-PCR. Patient characteristics are described in Table 1. Patient treated with TKI less than 3 months were excluded.

Scoring systems in CML

Three common prognostic scoring systems are available for CML patients prior to commencing therapy: (1) the Sokal (modification) score formula is defined as follow exp 0.0116 (age-43) + 0.0345 (spleen size[cm below costal margin] − 7.5 cm) + 0.188[(platelet count/700)^2 − 0.563] + 0.0887 (% blasts in blood - 2.1) and categorized as high score > 1.2, intermediate score 0.8-1.2, low score < 0.8, (2) the Hasford (modification) score formula is defined as follow (0.6666 × age [0 when age < 50 years; 1, otherwise] + 0.0420 × spleen size [cm below costal margin] + 0.0584 × blasts [%] + 0.0413 × eosinophils [%] + 0.2039 × basophils [0 when basophils < 3%; 1, otherwise] + 1.0956 × platelet count [0 when platelets < 1,500 × 109/L; 1, otherwise]) × 1,000 and categorized as high score > 1,480, intermediate score > 780 and < 1,480, low score < 780, (3) the European Treatment and Outcome Study (EUTOS) score is defined as follow 7 × basophils + 4 × spleen size as high score > 87 and low score < 87[5]. Sokal score (modified) is based on patient age and clinical characteristics including spleen size, platelet count, eosinophil count without calculating blast percentage. Hasford model (modification) also includes eosinophil and basophil counts and similar to Sokal score. The EUTOS score is defined only by basophil count and spleen size (in cm).

Ethics statement

The study was approved by Sanglah Hospital, Bali ethic committee. All patients data were handled according to ethical and legal standards. We obtained written informed consent from all participants involved in our study.

Statistical methods

Statistical analysis was performed using SPSS 17.0 (IBM). We performed normality test using Kolmogorov-Smirnov. Descriptive statistic test was performed to show patient characteristics. Correlation and comparation test using chi square (x^2) were used to determine the relationship between initial clinical and laboratory conditions with treatment response and relationship between Eutos, Sokal and Hasford scores with treatment response. A P-value < 0.05 was considered statistically significant.

Table 1 Background characteristics of the samples

Variable	N	%
Gender		
Male	25	62.5
Female	15	37.5
Age (years)		
< 20	3	7.5
20-29	10	25
30-39	14	35
40-49	8	20
50-59	3	7.5
> 60	2	5
Fever		
Yes	33	82.5
No	7	17.5
Weight loss		
Yes	40	100
No	0	0
Anemia		
Yes	30	75
No	10	25
Bleeding		
Yes	7	17.5
No	33	82.5
Splenomegaly		
Yes	39	97.5
No	1	2.5
Treatment regiment		
Hydrea, Imatinib	19	47.5
Hydrea, Nilotinib	10	25
Imatinib	1	2.5
Nilotinib	3	7.5
Imatinib, Nilotinib	3	7.5
Hydrea, Imatinib, Nilotinib	4	10

Results

Characteristics of the CP-CML subjects

A total 40 samples with CP-CML who met the inclusion and exclusion criteria were enrolled in this study. Of the 40 patients, there were 25 men (62.5%) and 15 women (37.5%). Patients who took part in this study aged 18-75 years and the mean age was 37 years. All samples have been using TKI therapy, namely imatinib or nilotinib ≥ 3 months. The most common clinical manifestation was weight loss (100%), followed by splenomegaly experienced by 39 people (97.5%). A total of 27 patients received imatinib as a first-line TKI

Table 2 Side effects of TKI in CP-CML patients

Side Effects	Imatinib (n = 20)	Nilotinib (n = 20)	Total (n = 40) %
Non Hematology			
Nausea	14	12	26 (65)
Myalgia	8	12	20 (50)
Hyperpigmentation	4	1	5 (12.5)
Headache	1	-	1 (2.5)
Rash	-	3	3 (7.5)
Hematology			
Anemia	4	5	9 (22.5)
Thrombocytopenia	8	7	15 (37.5)
Neutropenia	3	2	5 (12.5)

TKI: tyrosine kinase inhibitors, CP-CML: chronic phase-chronic myeloid leukemia.

treatment, 7 of the 27 patients then continued therapy with nilotinib for several reasons. There were 13 patients who received nilotinib as first-line TKI therapy. Hydroxyurea was administered to 33 patients before TKI therapy was administered, 22 patients then received imatinib and the rest received nilotinib. In all patients, the dose of imatinib received was 400 mg and the dose of nilotinib was 600 mg per day. Table 1 presents the background characteristics of the patients.

Side effects after taking TKI therapy are divided into non-hematological and hematological. The most common non-hematological effect felt by patients was nausea, as many as 26 patients (65%). Meanwhile, the most common hematological effect was thrombocytopenia, experienced by 15 patients (37.9%). Based on the type of TKI therapy received, patients receiving imatinib therapy most often experienced nausea, as many as 14 patients (70%). The most common effects in patients with nilotinib were nausea and myalgia, in 12 patients (60%) each. The most common hematologic side effect in both the imatinib and nilotinib groups was thrombocytopenia, in 8 (40%) and 7 (35%). Table 2 presents the side effects of TKI in CP-CML patients.

Hematological response to treatment

CHR is defined when laboratory markers return to normal levels and the absence of extramedullary involvement (spleen size return to normal size). Data for the CHR assessment are presented in Table 3. Complete blood counts (CBC) were taken every 3, 6, 9 and 12 months after therapy. At baseline, the mean leukocyte was 208,250/mm^3 and after 3 months of therapy, the mean was 42,651/mm^3. The initial average hemoglobin (Hb) was 9.86 g/dL and after 3 months it was 11.43 g/dL. The mean of initial platelets was 459,398/mm^3 and after 3 months it became 290,825/mm^3. The results of CBC in CML patients treated with TKI can also be seen in Fig. 1. CHR after 3 months of TKI therapy was achieved by 15 patients (37.5%). Meanwhile, after the 6th month of therapy, the number of patients who achieved CHR increased to 19 patients (47.5%) (Table 4).

Table 3 Complete Blood Count Profile

Peripheral Blood Parameter	Mean ± SD
Leucocyte (× 10^3/mm^3)	
Initial baseline	208.25 ± 112.69
3 months treatment	42.65 ± 52.82
6 months treatment	20.83 ± 28.90
9 months treatment	16.18 ± 29.67
12 months treatment	9.07 ± 9.60
Haemoglobin (g/dL)	
Initial baseline	9.86 ± 2.48
3 months treatment	11.43 ± 2.05
6 months treatment	12.12 ± 2.02
9 months treatment	10.61 ± 4.86
12 months treatment	12.26 ± 2.05
Platelet (× 10^3/mm^3)	
Initial baseline	459.39 ± 431.60
3 months treatment	290.82 ± 251.44
6 months treatment	232.83 ± 207.99
9 months treatment	164.40 ± 127.39
12 months treatment	239.10 ± 156.10
Absolute basophil (× 10^3/mm^3)	
Initial baseline	10.66 ± 15.95
3 months treatment	1.20 ± 2.47
6 months treatment	0.30 ± 0.99
9 months treatment	0.04 ± 0.09
12 months treatment	0.07 ± 0.16
Basophil (%)	
Initial baseline	4.47 ± 4.18
3 months treatment	1.94 ± 2.29
6 months treatment	0.83 ± 1.00
9 months treatment	0.51 ± 0.88
12 months treatment	1.17 ± 1.92

Molecular treatment response

MMR is defined when BCR-ABL is less than 0.1% in quantitative RT-PCR of blood cells. The MMR is a safe phase during treatment and should be achieved within 18 months (ideally after 12 months of TKI) and should

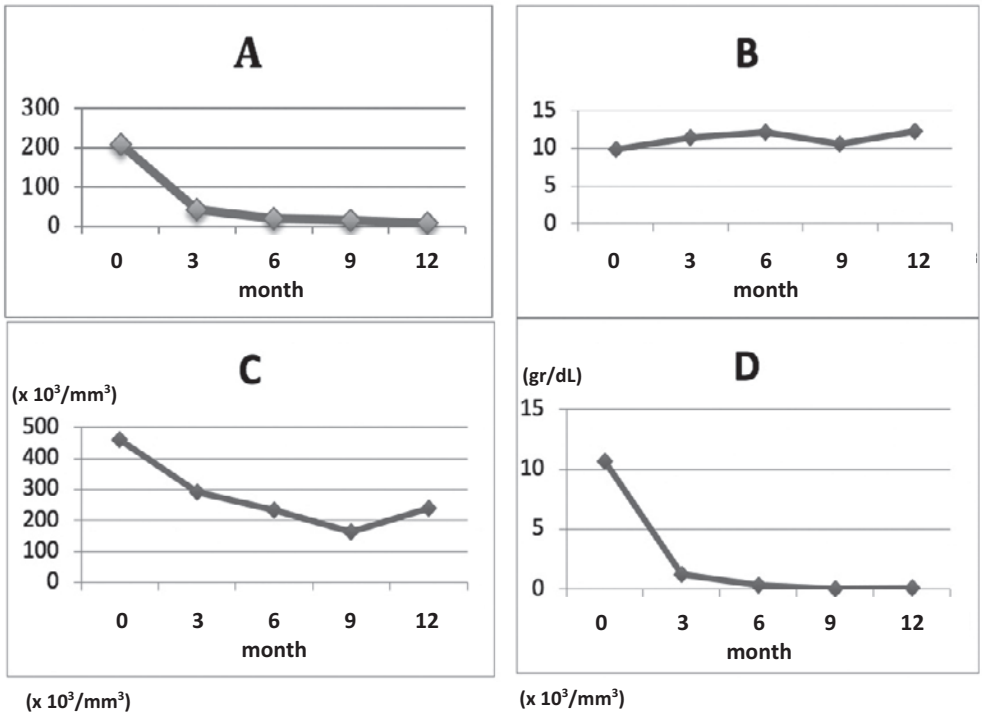

Figure 1 Hematological profile of patients treated with TKI agent after 3, 6, 9 and 12 months. **A** Leucocyte (× 10^3/mm^3), **B** Hemoglobin (gr/dL), **C** Platelet (× 10^3/mm^3), **D** Basophil (× 10^3/mm^3)

Table 4 *Complete Hematologic Response* (CHR) during 3rd and 6th months TKI treatment

Complete Hematologic Response (CHR)	3rd months (n, %)	6th months (n, %)
Achieved, n (%)	15 (37.5)	19 (47.5)
Imatinib	9	10
Nilotinib	6	9
Not achieved, n (%)	25 (62.5)	21 (52.5)
Imatinib	11	10
Nilotinib	14	11

Table 5 Proportion of patients who achieved MMR after 12 months treatment based on type of TKI

TKI Regiment	MMR after 12 months treatment (n = 37)	
	Yes (n = 20; %)	No (n = 17; %)
Imatinib	9 (24.3)	10 (27.0)
Nilotinib	11 (29.7)	7 (18.9)

TKI: tyrosine kinase inhibitors, MMR: major molecular response.

be maintained throughout the long-term management of CML. In this study, from 37 samples who performed quantitative BCR-ABL examination, 20 patients (54%) achieved MMR, and the remaining 17 (45.9%) had not achieved MMR. The proportion of patients who achieved a major molecular response based on the type of tyrosine kinase inhibitor used is shown in Table 5.

Relationship between initial clinical symptoms and laboratory markers with treatment response

We found no significant relationship between the initial clinical symptoms, such as fever, weight loss, anemia syndrome, bleeding, and splenomegaly with the therapeutic response achieved which is hematological and molecular response after third and fourth months of treatment. Meanwhile, correlation test was also carried out to determine the relationship between laboratory markers (leukocyte, hemoglobin, platelet and basophil levels) at the beginning of therapy and after the third month of therapy with the treatment response. We found a significant relationship between basophil (%) in the third month of treatment and BCR ABL quantitative levels ($p < 0.05$). Linear regression test was performed to determine the relationship of several laboratory markers with quantitative BCR-ABL levels,

Table 6 Proportion of patients who achieved CHR after 3rd and 6th months treatment based prognostic score

Score	CHR after 3rd months (n = 40)		CHR after 6th months (n = 40)	
	Yes (n = 15; %)	No (n = 25; %)	Yes (n = 19; %)	No (n = 21; %)
Eutos				
Low (≤ 87)	6 (15)	10 (25)	9 (22.5)	7 (17.5)
High (> 87)	9 (22.5)	15 (37.5)	10 (25)	14 (35)
Sokal				
Low (< 0.8)	12 (30)	23 (57.5)	16 (40)	19 (47.5)
Intermediate (0.8-1.2)	1 (2.5)	2 (5)	1 (2.5)	2 (5)
High (> 1.2)	2 (5)	-	2 (5)	-
Hasford				
Low (≤ 780)	12 (30)	23 (57.5)	16 (40)	19 (47.5)
Intermediate (781-1,480)	2 (5)	2 (5)	2 (5)	2 (5)
High (> 1,480)	1 (2.5)	-	1 (2.5)	-

CHR: complete hematologic response.

Table 7 Proportion of patients who achieved MMR after 12th months treatment based prognostic score

Score	MMR after 12th months treatment (n = 37)	
	Yes (n = 20; %)	No (n = 17; %)
Eutos		
Low (≤ 87)	8 (39.1)	7 (41.2)
High (> 87)	12 (60.9)	10 (58.8)
Sokal		
Low (< 0.8)	19 (95)	15 (88.2)
Intermediate (0.8-1.2)	1 (5)	1 (5.9)
High (> 1.2)	-	1 (5.9)
Hasford		
Low (≤ 780)	19 (95)	14 (82.4)
Intermediate (780-1,480)	1 (5)	2 (11.8)
High (> 1,480)	-	1 (5.9)

MMR: major molecular response.

and basophils level is the only significant variables that correlated with BCR ABL quantitative (p value = 0.017).

Relationship between Eutos, Sokal and Hasford Scores with therapeutic response in CP-CML patients

Therapeutic response that evaluated was the hematological response at the third and sixth months, as well as the achievement of MMR after administration of TKI after 12 months. Chi Square test was performed to find the relationship between the three prognostic scores (Eutos, Sokal and Hasford) and the response to therapy, there was no significant relationship between these prognostic scores and hematological and molecular therapy response. The proportion of patients based on Eutos, Sokal and Hasford scores who achieved a response to therapy can be seen in Tables 6 and 7.

Discussion

Our study found the average age was 37 years old. The study conducted by Reksodiputro et al. in 2011 in 21 patients at Rumah Sakit Umum Pusat Nasional Dr. Cipto Mangunkusumo Jakarta also found similar average age (36 years)[6]. Compared with other studies conducted outside Indonesia, the age of CML patients in Indonesia is relatively younger. Two studies conducted in European countries showed the median age of CML patients was 46 and 48 years, while there were 3 studies conducted in the USA showed the median age ranged from 56-58 years old[7,8]. In our study, there was only 1 patient aged > 60 years old (75 years old) and the youngest patient was 18 years old. The age range in other studies outside Indonesia reached the age of the oldest patient 85 years with the youngest age similar to our study. Observing some of the comparisons above, researchers suspect the differences are due to genetic influences[9]. Differences in life expectancy can also affect the age of CML patient in certain country.

The most common CML manifestation in our study was weight loss and the second was splenomegaly

which occurred in 39 patients. The percentage of splenomegaly in our study was 97.5%, which is higher compared to several other studies with an average percentage of splenomegaly only occurred in less than 50% patients[8]. This probably because most of our patients came with more severe conditions, one of them is enlarged spleen, while in another study, CML was found incidentally during a routine complete blood count.

The mean leukocyte count of CML patients in our study was 208,250/mm^3, which was higher than median leukocyte in study by Reksodiputro et al. (2011) which is 13,300/mm^3. Lavallade et al. (2008) found that the median leukocyte was 140,000/mm^3 among 204 CML patients with an interval since diagnosis of 1.7 months[6]. The possibility of this difference is caused by the complete blood data in our study was taken based on the earliest available data in the medical record where the leukocyte level was still very high. The severity of the disease and the use of Hydrea also affect leukocyte levels. Hydrea helps reduce leukocytes before TKI therapy is started. The median Hb in our study was slightly lower than the study conducted by Reksodiputro et al. (2011), but slightly different from the study conducted by O'Dwyer et al. (2004) and Lavallade et al. (2008). Both studies had median Hb of 12.5 g/dL and 11.6 g/dL[6,10]. This difference may be due to racial factors. According to Bakta (2006), the cut-off point of Hb in Indonesia to determine anemia is 10 g/dL, while universally the cut-off point of 12 g/dL is more widely used. Furthermore, the correlation study by Kantarjain et al. (2002) stated that Hb > 12 g/dL had a significant positive effect on the cytogenetic response of CML patients. According to O'Dwyer (2004), CML patients with Hb > 12 has lower risk of hematological relapse. The median platelet count in our study was 338,000/mm^3 and similar to several other studies which is < 450,000/mm^3 [3,7,8,10].

Based on ELN recommendations in 2013, CHR should be achieved in 3 months after TKI therapy and maintained for at least 4 weeks. CHR must continuously maintained from the 3rd month to the 6th, 9th, and 12th months so it will have better prognosis for next CML disease progression. CHR that is not achieved in all these months is a clear indication of disease progression. In our study, CHR at 3 months was achieved in 15 of 40 patients, or approximately 37.5%. The reason for this low percentage of CHR is probably due to the high baseline leukocyte levels in our study. A high leukocyte count indicates a higher disease severity, resulting in a lower percentage of patients who can achieve CHR within 3 months. When compared with other studies with leukocyte counts still in the range < 50,000/mm^3, it will certainly produce very different outcomes if using the same CHR criteria.

Based on the type of therapy received, 9 (45%) of the 20 patients treated with imatinib and 6 (30%) of the 20 patients treated with nilotinib achieved CHR at 3 months after therapy. A study by Reksodiputro et al in 2010 in CML patients treated with imatinib and a median initial leukocyte of 13,300/mm^3, 3-months CHR was achieved by 74% of patients. By the same authors, in a 2011 study with a median leukocyte count of 74,000/mm^3, 3-month CHR was achieved by 36.8% with imatinib therapy[6]. This supports the assumption that high initial leukocyte levels greatly affect the patient's hematological response[6]. In the study by Kantarjian et al (2002), of 454 CML patients with imatinib, 95% achieved CHR within 3 months. Similarly, in the study by Cortes et al (2005), of 305 CML patients on imatinib, 96% achieved CHR at 3 months[7]. Those two previously mentioned studies had baseline leukocyte counts < 20,000/mm^3. Compared to that study, the percentage of achieving CHR in nilotinib patients in our study was lower. However, this needs to be re-evaluated considering the number of patients in our study is small so it is not quite comparable[7,8,10].

ENESTnd compared imatinib and nilotinib in CML patients and reported that nilotinib was superior to imatinib, as indicated by a higher percentage of achievement in all parameters of therapeutic response (hematological, cytological, and molecular) in nilotinib[11]. The percentage of CHR of nilotinib patients in our study was higher in imatinib patients but further studies need to be done on the significance of the difference because our sample size was too small and the number of sample was same in the both treatment groups. Low achievement of CHR in our study may be also probably due to bad-adherence in some patients and may be due to the presence of leukocytosis due to other causes such as inflammatory processes or infectious processes.

We found higher percentage of nausea as side effects in imatinib, while myalgia had a higher percentage in nilotinib patients. This is slightly different from the results of the ENESTnd study on the side effects of imatinib and nilotinib which reported more frequent incidences of nausea and myalgia in patients taking imatinib[12]. In terms of hematological side effects, the ENESTnd study reported more thrombocytopenia in patients taking nilotinib and neutropenia more frequently in subjects taking imatinib. Hematological side effects in our study were comparable to those of the ENESTnd study.

The prevalence of patients achieving MMR in our study was 20 out of a total of 37 patients (54%). Most of the samples who achieved MMR were treated with nilotinib compared to imatinib (29.7% vs 24.3%). Although the difference was not significant, this result was similar to the ENESTnd study, where the MMR obtained in each group with imatinib 400 mg OD, nilotinib 300 mg BID, and nilotinib 400 mg BID were 17%, 44% and 32%, respectively. MMR was significantly higher in the nilotinib group compared to the imatinib group, 52.2% vs 27.8%; $p < 0.0001$[13]. The cause of the low achievement of MMR in both groups of our patients (imatinib and nilotinib) is very likely due to several factors such as inadequate medication adherence, or the possibility of mutations that is difficult to prove due to the absence of facilities.

Our study found significant relationship between basophil percentage levels at month 3 and quantitative BCR-ABL levels. This result is similar with the study conducted in Canada conducted by Denburg JA, et al. where increase in basophil is a poor prognosis for patients with CML. Their study involved 47 CP-CML patients who were evaluated for basophil growth and differentiation in vitro. The data showed that there is a relationship between basophil Growth Index (BGI) and the clinical time of the onset of the blastic phase as well as the overall survival rate. And to confirm these results, a study with a larger sample size scale found that BGI was correlated with death or the occurrence of the blastic phase within 2 years ($p < 0.01$), with a sensitivity of 78%, specificity of 81%, positive predictive value of 64%, and negative predictive value 89%. This finding strengthens the prognostic value of basophil growth assays in CML patients[14].

Although some pilot studies such as IRIS, ENESTnd and DASISION showed fairly strong prognostic value from the existing scoring system, such as Eutos, Sokal and Hasford scores, our study showed that there was no significant relationship between these prognostic scores and hematological and molecular responses to therapy, both hematological and molecular therapy. A study with a larger sample size is needed to re-examine whether the existing scoring system can be applied to CP-CML patients treated at the Internal Medicine Polyclinic, Sanglah Hospital Denpasar.

In conclusion, Eutos, Sokal and Hasford prognostic scores were not associated with hematological response to therapy at 3, 6 months or major molecular response after 12 months. It is suggested that basophil percentage at three months treatment is predictive factor for quantitative BCR-ABL levels. Further studies are needed to deal with the limitations of the present study, i.e., larger size sample to represent CML patients treated with TKI treatment in Sanglah Hospital so that in the future it can be applied as predictive factors in daily practice.

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