Therapeutic Responses of Imatinib and Nilotinib among CML Patients in Hasan Sadikin Hospital Bandung

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ABSTRACT

Introduction: Chronic Myeloid Leukemia (CML) is a myeloproliferative malignancy with an estimated incidence in the world of 1-2 cases per 100,000 adults. The use of Tyrosine Kinase Inhibitors (TKI) as a therapy for CML is still the first choice for treatment, but some cases show a high level of resistance or intolerance to TKI therapy. This study aims to identify the therapeutic responses of imatinib and nilotinib among CML patients in Bandung.

Method: This study is an analytical descriptive study of CML patients at Hasan Sadikin Hospital’s Hematology and Medical Oncology Outpatient Clinic in 2017. The total number of samples in this study is 244 patients, consisting of 199 patients with Imatinib therapy and 45 patients with Nilotinib therapy. The data is processed using SPSS Statistics 22.0 software.

Result: The results showed that CML patients had a median age of 42 years, sex ratio of 1:1 and the highest prevalence was in Bandung City (21.3%). Hematologic response is dominated by complete hematologic response, as high as 72.86% with Imatinib and 66.67% with Nilotinib. Molecular response 3-6 months post therapy is dominated by suboptimal response in as many as 36.8% with Imatinib and failure in as many as 50% with Nilotinib. Molecular response 12-18 months post therapy is dominated by failure in as high as 69.4% with Imatinib and 52.4% with Nilotinib.

Conclusion: Based on the molecular response, the rates of suboptimal response and resistance are quite high. Regular monitoring standards of therapy for CML patients are needed to identify TKI resistance so alternative therapies can be provided to improve the outcomes.

INTRODUCTION

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm with a worldwide incidence of 1 – 2 cases per 100,000 adults. Around 15% of CML cases are diagnosed in adulthood. In 2015, 7,000 new cases of CML were diagnosed in USA causing around 1.100 deaths (1). Chronic Myeloid Leukemia is caused by the translocation between BCR gene in chromosome 22 and ABL gene in chromosome 9. This reciprocal translocation forms Philadelphia chromosome (t 9;22) which produces the unique BCR-ABL protein. The protein that is formed relates to the kinase activity causing uncontrolled hematopoietic stem cells proliferation (2,3). The management of CML significantly changed with the development of Tyrosine Kinase Inhibitors (TKI) molecules that have the potential to intervene the interaction between oncoprotein BCR-ABL and Adenosine Triphosphate (ATP), leading to inhibition of neoplastic cellular proliferation (4).

The use of TKI as the main therapy for CML is caused by its high effectiveness. However, nowadays, a few cases of CML showed resistance to TKI therapy, up to 1 per 3
TKI resistance is defined by the inability of TKI drug to achieve pharmacological target, caused by the drug itself or by other factors acting as obstacles to achieve the treatment target (4). Resistance to TKI can be evaluated by hematologic response, cytogenetic response, and molecular response after a certain amount of time (5,6).

From a multicentre study in Indonesia, the rate of resistance to TKI is higher (47.69%) than in Europe (around 24%) (7,8). Until now in Indonesia, specifically in West Java there has not been any study describing resistance to TKI, in patients using first-line drug (imatinib) and patients using second-line drug (nilotinib). Based on the description above, this study will review the TKI (imatinib and nilotinib)-resistant Chronic Myeloid Leukemia patients in Hasan Sadikin Hospital Bandung.

METHODS

This study is an analytical descriptive study with the target population of CML patients in Hasan Sadikin Hospital. The subjects of this study were CML patients at Hasan Sadikin Hospital’s Hematology and Medical Oncology Outpatient Clinic in 2017, taken as secondary data from patients’ medical records with the inclusion criteria of BCR-ABL examination done in 2015-2017 and those with complete medical records data.

The characteristics reviewed including age, sex, domicile, TKI being used, BCR-ABL value when first diagnosed, hematologic response from TKI, and molecular response from TKI. Hematologic response was assessed with routine blood check for 3 months after TKI therapy. Complete hematologic response is indicated by normal leucocytes and thrombocytes counts, intolerance is indicated by leucocyte count of <4x10^9/L and/or thrombocyte count of <150x10^9/L, and failure response is indicated by leucocytosis and thrombocytosis (6,9).

Molecular response was assessed by BCR-ABL examination with Polymerase Chain Reaction (PCR) method. Patients with BCR-ABL value in 3-6 months after TKI therapy were then categorized into three categories: early molecular response (EMR) (BCR-ABL ≤ 10%), suboptimal (with decreasing BCR-ABL value), and failure in achieving EMR (neither decreasing nor increasing BCR-ABL value). Patients with BCR-ABL value in 12-18 months after TKI therapy were then categorized into three categories: complete molecular response (BCR-ABL not detected), major molecular response (BCR-ABL value < 0.1% or decrement of ≥ 3 log), and failure (neither decreasing nor increasing BCR-ABL value) (6,9). Data was processed using SPSS Statistic 22.0 software. For numerical data, p value was tested by One Way ANOVA test if the data was normally distributed. Categorical data p value was calculated based on the Chi-Square test with an alternative of Kolmogorov-Smirnov and Exact test. Value of significance based on p value <0.05 (10,11).

RESULTS

During the study period, there were 301 CML patients at Hasan Sadikin Hospital’s Hematology and Medical Oncology Outpatient Clinic in 2017, but only 244 of these patients fulfilled the criteria for this study.

The ratio of women to men was 1:1. The median age of CML patients was 42 years. Most of these CML patients lived in Bandung City (21.3%). As many as 199 patients used Imatinib and 45 patients used Nilotinib. The mean of BCR-ABL value on the first diagnosis was 28.40±40.733% (Table 1).

Table 1. CML patients characteristics (N = 244)

| Characteristics            | Value          |
|---------------------------|----------------|
| Age (years)               | Mean ± SD      |
|                           | 41.5±13.5      |
|                           | Median         |
|                           | 42.00          |
|                           | Range (min-max)|
|                           | 15.0-79.0      |
| Sex                       | Male           |
|                           | 122 (50%)      |
|                           | Female         |
|                           | 122 (50%)      |
| Domicile: N (%)           |                |
| Bandung City              | 52 (21.3%)     |
| Bandung Regency           | 40 (16.4%)     |
| Sumedang Regency          | 17 (7%)        |
| Subang Regency            | 13 (5.3%)      |
| Sukabumi Regency          | 12 (4.9%)      |
| Bandung Barat Regency     | 11 (4.5%)      |
| Garut Regency             | 11 (4.5%)      |
| Cimahi City               | 11 (4.5%)      |
| Tasikmalaya Regency       | 10 (4.1%)      |
| Majalengka Regency        | 9 (3.7%)       |
| Ciamis Regency            | 8 (3.3%)       |
| Indramayu Regency         | 8 (3.3%)       |
| Karawang Regency          | 7 (2.9%)       |
| Cianjur Regency           | 6 (2.5%)       |
| Purwakarta Regency        | 6 (2.5%)       |
| Cirebon City/ Regency     | 5 (2.0%)       |
| Tasikmalaya City          | 4 (1.6%)       |
| Bekasi Regency            | 3 (1.2%)       |
| Other Cities/ Regencies   | 11 (4.5%)      |
| Therapy given: N (%)      |                |
| Imatinib                  | 199 (81.6%)    |
| Nilotinib                 | 45 (18.4%)     |
| BCR-ABL value (First time diagnosed): % | |
| Mean±SD                   | 28.4±40.7      |
| Median                    | 13.64          |
| Range (min-max)           | 0.0-259.2      |
In the Imatinib group, average age was 41.12 ± 13.694, with 49.7% male patients and 50.3% female patients. In the Nilotinib group, average age was 43.26 ± 12.897, with 51.1% male patients and 48.9% female patients. TKI therapy showed good hematologic response, characterized by the amount of complete hematologic response in as many as 72.9% with Imatinib, and 66.7% with Nilotinib. While failure to achieve hematologic response was seen in 23.3% with Imatinib, and 33.3% with Nilotinib (Table 2).

Molecular responses were assessed in 3-6 months post therapy (38 patients with Imatinib and 8 patients with Nilotinib) and 12-18 months post therapy (72 patients with Imatinib and 21 patients with Nilotinib). As many as 89 patients with Imatinib and 16 patients with Nilotinib were excluded because the BCR-ABL examination in Hasan Sadikin Hospital has not been carried out in accordance with the standard examination after the TKI therapy (Figure 1).

Table 2. Comparison of Age, Gender, Hematological Response and BCR ABL of Patients Given Therapy with Imatinib and Nilotinib

| Variable                  | Imatinib N=199 | Nilotinib N=45 | P Value |
|---------------------------|----------------|----------------|---------|
| Age (years)               |                |                |         |
| Mean±SD                   | 41.1±13.6      | 43.2±12.8      | 0.338   |
| Median                    | 41.0           | 46.0           |         |
| Range (min-max)           | 15.0-79.0      | 22.0-67.0      |         |
| Sex                       |                |                | 0.869   |
| Men                       | 99(49.7%)      | 23(51.1%)      |         |
| Women                     | 100(50.3%)     | 22(48.9%)      |         |
| Hematologic Response      |                |                | 0.208   |
| Complete                  | 145(72.9%)     | 30(66.7%)      |         |
| Intolerance               | 7(3.5%)        | 0(0.0%)        |         |
| Failure                   | 47(23.6%)      | 15(33.3%)      |         |
| BCR ABL                   |                |                | 0.242   |
| Mean±SD                   | 22.7±37.6      | 31.3±52.8      |         |
| Median                    | 14.8           | 3.6            |         |
| Range (min-max)           | 00.0-198.3     | 0.0-259.2      |         |

Figure 1. Diagram flow of CML patients based on molecular response
Failure to achieve molecular response due to resistance to Imatinib occurred in as many as 29% patients in 3-6 months. In these patients, the average age was 42.27 ± 12.977, mostly were men (72.7%), and there were statistically significant differences in the percentage of hematologic responses (p = 0.046) for the early molecular response, suboptimal and failed groups that were given Imatinib therapy for 3-6 months (Table 3).

Failure to achieve molecular response due to resistance to Imatinib occurred in as many as 69.4% patients in 12-18 months. The average age of these patients was 40.72 ± 12,530, and mostly were women (54%) (Table 4).

Table 3. Comparison of age, gender, hematologic responses and BCR ABL in the early molecular response, suboptimal and failed groups of patients given Imatinib for 3-6 months.

| Variable               | Early Molecular Response | Suboptimal | Failure | P Value |
|------------------------|--------------------------|------------|---------|---------|
|                        | N=13 (34.2%)             | N=14 (36.8%)| N=11 (29%)|         |
| Age (years)            |                          |            |         |         |
| Mean ± SD              | 40.3±20.0                | 33.8±10.5  | 42.2±12.9| 0.341   |
| Median                 | 36.0                     | 33.0       | 46.0    |         |
| Range (min-max)        | 17.0-79.0                | 17.0-56.0  | 21.0-60.0|         |
| Sex                    |                          |            |         | 0.487   |
| Men                    | 7(53.8%)                 | 7(50.0%)   | 8(72.7%)|         |
| Women                  | 6(46.2%)                 | 7(50.0%)   | 3(27.3%)|         |
| Hematologic Response   |                          |            |         | 0.046** |
| Complete               | 12(92.3%)                | 6(42.9%)   | 8(72.7%)|         |
| Intolerance            | 1(7.7%)                  | 1(7.1%)    | 0(0.0%) |         |
| Failure                | 0(0.0%)                  | 7(50.0%)   | 3(27.3%)|         |

Table 4. Comparison of age, gender, hematologic response and BCR ABL in the complete molecular response group, major molecular response and failed patients given Imatinib for 12-18 months.

| Variable               | Complete Molecular Response | Major Molecular Response | Failure | P Value |
|------------------------|------------------------------|--------------------------|---------|---------|
|                        | N=12 (16.7%)                | N=10 (13.9%)             | N=50 (69.4%)|         |
| Age (years)            |                             |                         |         | 0.176   |
| Mean ± SD              | 36.0±11.6                   | 46.8±18.7               | 40.7±12.5|         |
| Median                 | 37.0                        | 51.0                    | 40.5    |         |
| Range (min-max)        | 18.0-57.0                   | 16.0-70.0               | 17.0-69.0|         |
| Sex                    |                             |                         |         | 0.333   |
| Men                    | 7(58.3%)                    | 7(70.0%)                | 23(46.0%)|         |
| Women                  | 5(41.7%)                    | 3(30.0%)                | 27(54.0%)|         |
| Hematologic Response   |                             |                         |         | 0.152   |
| Complete               | 12(100.0%)                  | 9(90.0%)                | 34(68.0%)|         |
| Intolerance            | 0(0.0%)                     | 0(0.0%)                 | 1(2.0%)  |         |
| Failure                | 0(0.0%)                     | 7(50.0%)                | 15(30.0%)|         |

Failure to achieve molecular response due to resistance to Nilotinib was observed in as many as 50% patients in 3-6 months, with the average age was 40.75 ± 9.105, and most of them were men (75%) (Table 5).

Failure to achieve molecular response due to resistance to Nilotinib was observed in as many as 52.4% patients in 12-18 months, with the average age was 43.72 ± 12,634, and predominantly men (54.5%) (Table 6).
Table 5. Comparison of age, gender, hematologic response and BCR ABL in the early molecular response, suboptimal and failed group of patients given Nilotinib for 3-6 months.

| Variable             | Group                  | P Value |
|----------------------|------------------------|---------|
|                      | Early Molecular        |         |
|                      | Response               |         |
|                      | N=2 (25%)              |         |
| Age (years)          | Mean ± SD              | 48.0±15.5 | 33.5±0.7 | 40.7±9.1 | 0.410 |
|                      | Median                 | 48.0     | 33.5     | 41.5     |         |
|                      | Range (min-max)        | 37.0-59.0 | 33.0-34.0 | 31.0-49.0 |         |
| Sex                  | Men                    | 1(50.0%) | 2(100.0%) | 3(75.0%) | 0.513 |
|                      | Women                  | 1(50.0%) | 0(0.0%)  | 1(25.0%) |         |
| Hematologic Response | Complete               | 1(50.0%) | 2(100.0%) | 1(25.0%) | 0.223 |
|                      | Intolerance            | 0(0.0%)  | 0(0.0%)  | 0(0.0%)  |         |
|                      | Failure                | 1(50.0%) | 0(0.0%)  | 3(75.0%) |         |

Table 6. Comparison of age, gender, hematologic response and BCR ABL in the complete molecular response group, major molecular response and failed groups in patients given Nilotinib for 12-18 months.

| Variable             | Group                  | P Value |
|----------------------|------------------------|---------|
|                      | Complete Molecular     |         |
|                      | Response               |         |
|                      | N=6 (28.6%)            |         |
| Age (years)          | Mean ± SD              | 54.5±6.4 | 35.7±20.5 | 43.7±12.6 | 0.059 |
|                      | Median                 | 53.0     | 27.5     | 45.0     |         |
|                      | Range (min-max)        | 48.0-67.0 | 22.0-66.0 | 22.0-64.0 |         |
| Sex                  | Men                    | 1(16.7%) | 2(50.0%)  | 6(54.5%)  | 0.305 |
|                      | Women                  | 5(83.3%) | 2(50.0%)  | 5(45.5%)  |         |
| Hematologic Response | Complete               | 5(83.3%) | 4(100.0%) | 6(54.5%)  | 0.169 |
|                      | Intolerance            | 0(0.0%)  | 0(0.0%)  | 0(0.0%)  |         |
|                      | Failure                | 1(16.7%) | 0(0.0%)  | 5(45.5%)  |         |

DISCUSSION

In this study we obtained samples as many as 244 patients. Within CML patients around the world, including Asia and Indonesia, the cases occur more often in male than female (8). But the result of our study showed equal percentages in male and female patients. The median of age for CML cases in the world is 65 years old, while in Indonesia the median of age for CML cases is 36 years old, similar to the median of age for CML cases in Asia (8). But in this study we found that the median of age was 42 years old.

Based on the domicile in West Java, five areas with most CML patients visiting the Outpatient Department of Hematology and Medical Oncology in Hasan Sadikin Hospital in 2017 were Bandung City with 52 patients (21.3%), Bandung Regency with 40 patients (16.4%), Sumedang Regency with 17 patients (7%), Subang
Regency with 13 patients (5.3%) and Sukabumi Regency with 12 patients (4.9%). Based on the therapy given, 199 patients (81.6%) were given Imatinib, and 45 patients (18.4%) were given Nilotinib. Based on BCR-ABL value in the first examination, we found a median value of 25.77%, a mean of 40.83%, a minimum value of 0% (negative) and a maximum value of 286.07%.

American Cancer Society classifies treatment response in Chronic Myeloid Leukemia as hematologic response, cytogenetic response, and molecular response. Hematologic response is assessed from complete blood count in the first 3 months of treatment, cytogenetic response is assessed from bone marrow examination, and molecular response is assessed by PCR testing of BCR-ABL gene in 3-6 month and 12-18 month of therapy (6) European Leukemia also classifies suboptimal and failed molecular response criteria based on post-therapy time evaluation. (Table 7). In this study, the treatment responses were only evaluated by hematologic and molecular responses to Imatinib and Nilotinib.

Table 7. Criteria for suboptimal and failure responses according to European LeukemiaNet.

| Evaluation Time (Month) | Suboptimal Response | Failure |
|-------------------------|---------------------|---------|
| 0                       | -                   | Less than CHR |
| 3                       | No CyR (Ph+ >95%)   | -       |
| 6                       | Less than PCyR (Ph+ >35%) | No CyR (Ph+ >95%) |
| 12                      | PCyR (Ph+ 1% – 35%) | Less than PCyR (Ph+ >35%) |
| 18                      | Less than MMR | Less than CCyR |
| Any Time                | The loss of MMR, mutation of BCR-ABL | The loss of CHR, the loss of CCyR, mutation of BCR-ABL, CCA/Ph+ |

CHR = complete hematologic response (Thrombocyte < 450x10⁹/L; Leucocyte < 10x10⁹/L; differential count without immature granulocytes), CyR = cytogenic response, PCyR = Partial complete cytogenic response, CCyR = Complete cytogenetic response, MMR = Major molecular response (BCR-ABL <0.1, CCA/Ph+ clonal evolution)

The patients in this study showed high rate of complete hematologic response from TKI. Treatment response to Imatinib showed that as many as 145 patients (72.86%) experienced complete hematologic response, 7 patients (3.52%) experienced intolerance and 47 patients (23.52%) experienced failure. While treatment response to nilotinib as second-line drug showed that as many as 30 patients (66.67%) experienced complete hematologic response and as many as 15 patients (33.3%) experienced failure.

Based on the 3-6 months molecular response and 12-18 months post Imatinib and Nilotinib therapy, there were 89 data on Imatinib therapy and 16 data on Nilotinib therapy that cannot be assessed because the BCR-ABL examination in Hasan Sadikin Hospital was not routinely done in every patient (Figure 1).

Molecular responses based on BCR-ABL data in 3-6 months after Imatinib therapy found that 13 patients (34.2%) experienced an early molecular response, 14 patients (36.8%) experienced suboptimal and 11 patients (29%) experienced resistance or failure. In the failure group, the average age of patients was 42.27 ± 12.977, with the highest percentage occurring in men (72.7%) compared to women. There was no statistically significant difference in age (p = 0.341) and sex (p = 0.487) for the early molecular response, suboptimal and failed groups. However, there were statistically significant differences in hematologic responses (p = 0.046) for the early molecular response, suboptimal and failed groups. This means that the hematologic response is directly proportional to the early molecular response in 3-6 months evaluation of TKI in CML patient. Failure to achieve a hematologic response also means failure to achieve an early molecular response. This is similar to previous studies that stated complete hematologic response must be achieved within 3 months of therapy (6).

Based on BCR-ABL data in 12-18 months after Imatinib therapy, 12 patients (16.7%) experienced complete molecular response, 10 patients (13.9%) experienced major molecular response, and 50 patients (69.4%) experienced failure. In the failure group, the average age of patients was 40.72 ± 12.530, with the highest percentage occurring in women (54.0%) compared to men. There was no statistically significant differences in age (p = 0.176), sex (p = 0.333) and hematologic response (p = 0.152) for the complete molecular response group, major molecular response and failure groups.

Molecular response based on BCR-ABL data in 3-6 months after Nilotinib therapy found that 2 patients (25%) experienced an early molecular response, 2 patients (25%) experienced a suboptimal response and 4 patients (50%) experienced failure. In the failure group, the average age of patients was 40.75 ± 9.105, with the highest percentage occurring in men (75.0%) compared to women. There were no statistically significant differences in age (p = 0.410), sex (p = 0.513) and hematologic response (p = 0.223) for the early molecular response, suboptimal and failure groups.
Based on BCR-ABL data in 12-18 months after nilotinib therapy, 6 patients (28.6%) experienced complete molecular response, 4 patients (19%) experienced major molecular response, and 11 patients (52.4%) experienced failure. In the failure group, the average age of patients was 43.72 ± 12.634, with the highest percentage occurring in men (54.5%) compared to women. There were no statistically significant differences in age (p = 0.059), sex (p = 0.305) and hematologic response (p = 0.169) for the complete molecular response group, major molecular response and failure groups.

This study shows that Imatinib and Nilotinib have good response toward patients’ hematologic status. Based on molecular response in 12-18 months after therapy, resistance rate in Imatinib is higher than Nilotinib. This is similar to previous studies that stated Imatinib as a first-line standard treatment choice with increasing resistance frequency (3).

One of the articles explaining that in the last few years, resistance to Tyrosine Kinase Inhibitor has become a distinctive challenge in the management of Chronic Myeloid Leukemia. Knowledge is needed in identifying all of the resistance mechanisms in CML therapy, to optimize the use of various TKI and combination of TKI as a new drug that can specifically prevent leukemic stem cell transformation and eradicate CML disease (12,13).

CONCLUSION

Even though TKI therapy gives effective response based on the hematologic response, it still shows a quite high rate of suboptimal and resistance rate based on the molecular response. Regular monitoring standards of therapy for CML patients are needed to identify TKI resistance so that alternative therapies can be provided and improve outcomes.

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