Factors Associated with Achieving Hematological Response in CML (Chronic Myeloid Leukemia) Patient

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Factors Associated with Achieving Hematological Response in CML (Chronic Myeloid Leukemia) Patient

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Abstract

Background: The goal of CML therapy is to achieve complete hematological response first, then cytogenetic response andcomplete molecular response at the very end. Achieving a complete hematological response is the easiest and relatively inexpensive to detect. Several factors are thought to have an association with achieving hematological response. This study sought to determine the factors associated with achieving hematological response in CML patients

Method: We conducted an observational retrospective cohort study of CML patients at Wahidin Sudirohusodo Hospital and its network on 2018-2019 period. Diagnosis was done by positive BMP (Bone Marrow Punctie) results for CML, then a monthly blood check until a hematological response was achieved.

Results: There wer 39 research subjects, 19 male (48.7%) and 20 female (51.3%). No association found between age, gender and achievement of hematological response. Type of therapy was significantly correlated with the achievement of hematological response, with the highest number found in Nilotinib therapy compared to other group. (54,1%; p = 0.046) Subjects who achieve hematological response had a lower percentage of blast cells. (6.1% vs. 7.9% ; p = 0.016)

Conclusion: The use of Nilotinib therapy was significantly associated with a succesful achievement of hematological response. A lower percentage of blast cells was found in CML patients who achieved hematological response.

Keywords: *CML, factors, complete hematological response.*

Introduction

Chronic myelocytic leukemia (CML) is a chronic myeloproliferative disease caused by genetic defects obtained in pluripotent stem cells that are characterized by the presence of the philadelphia (Ph) chromosome with a main consequence as the fusion of ABL and BCR genes on chromosome 22.[1,2]

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CML is 14% of all leukemias and 20% of leukemia in adults. The incidence per year is 1.6 cases per 100,000 adults with a slightly dominant male. Data on CML in Indonesia in 2018 obtained 2,374 patients, mostly in the area of Surabaya as many as 516 patients, at least in Banda Aceh as many as 40 patients, in Makassar obtained a total of 110 pasien.[3]

The goal of CML therapy is to achieve complete hematological response at first, then cytogenetic response and complete molecular response at the very end.[4,5] Achieving a complete hematological response is the easiest and relatively inexpensive to detect. Several factors are associated with the achievement of hematological response. Singh and colleagues

stated older age and female sex were related witha poor achievement of haematological, cytogenetic and prognostic responses.[6] Type of therapy also has an association with achieving hematological response. Breakthroughs in molecular targets of tyrosine kinase inhibitor (TKI) have brought changes in the history of disease and in therapeutic approaches to the treatment of CML patients. The high percentage of blast cells number is a poor prognostic factor and hematological response in CML disease. We sought to study various factors associated with achievement of hematological response in CML patients

Method

This study was a retrospective cohort study by observational analysis of CML patients at Wahidin Sudirohusodo Hospital Makassar, on the period of 2018-2019. Inclusion criteria were CML patient, age ≥ 18 year. Exclusion criteria were (1) Othermyeloproliferative diseases (2) Patients with acute infections. CML diagnosis were done by BMP (Bone Marrow Punctie) analysis showing CML pattern.

The types of therapy given to the subjects of this study were the hydroxy urea, imatinib and nilotinib. The percentage of blast cells obtained from BMP results at the beginning of the study. Monthly Complete Blood Count and differential count examination was done until a complete hematological response is achieved (Platelets ≤ 450 x 109 / L, Leukocytes ≤ 10 x 109 / L, and normal differential count) Statistical analysis was done using *Statistical Package for Social Science* (SPSS) v.22 (IBM®) with 95% confidence interval. Non parametric analyses was done using *fisher test* and *Mann Whittney U test* for comparison between groups.

Results

Baseline characteristics of the 39 study subjects are displayed on Table 1. Female gender predominates over male gender (51,3% vs. 48.7% respectively). The mean age was 40.2 ± 13.3 years.

Table 1. Baseline Characteristics of The Study Subjects

Variable		n	%
Gender	Male	19	48,7
	Female	20	51,3
Type of Therapy	Hydroxy Urea	14	35,9
	Imatinib	8	20,5
	Nilotinib	17	43,6
CML Phase	Chronic Phase	36	92,3
	Acceleration Phase	1	2,6
	Remission Phase	2	5,1
Hematological Response	Achieved	24	40,9
	Not Achieved	15	39,1

Table 2. Baseline Hematological Characteristics of The Study Subjects

Variable	Minimum	Maximum	Mean	Std. Deviation
Blast Cell (%)	2	15	6,8	2,3
Leucocyte	1.400	163.700	2.5587,2	36.141,2
Trombocyte	35.000	1.083.000	277.284,6	242.183,4

The types of therapy given consisted of Hydroxy Urea to 14 study subjects (35.9%), Imatinib to 8 research subjects (20.5%), and Nilotinib to 17 research subjects (43.6%). In this study, 36 research subjects (92.3%) experienced chronic phase CML, 1 research subject (2.6%) experienced acceleration phase CML, and as many as 2 research subjects experienced remission phase CML (5.1%). Achievement of hematological responses in research subjects by 24 research subjects (40.9%), and that was not achieved by 15 research subjects (39.1%).

Table 2 shows the percentage of Blast cells ranging from 2-15% with an average of 6.8 ± 2.3%. The number of leukocytes ranged from 1.400 - 163.700 with an average of 25.587.2 ± 36.141,2. Platelet counts ranged from 35.000-1.083.000 with an average of 277.284,6 ± 242.183,4.

Table 3. Association between age group and hematological response achievement

Age		Hematological Response		Total	p (C.I. 95%)
		Achieved	Not Achieved		
< 40 years old	n	12	9	21	0,542
	%	57,1%	42,9%	100,0%	
≥ 40 years old	n	12	6	18	
	%	66,7%	33,3%	100,0%	
Total	n	24	15	39	
	%	61,5%	38,5%	100,0%	

Table 3 shows the achievement of hematological response at age ≥ 40 years was higher than at age <40 years (66.7% vs. 57.1% respectively). However, no significant association was found between age and hematologic responses achievement (p = 0.542).

Table 4. Association Between Gender and Hematological Response Achievement

Gender		Hematological Response		Total	p (C.I. 95%)
		Achieved	Not Achieved		
Male	n	11	8	19	0,648
	%	57,9%	42,1%	100,0%	
Female	n	13	7	20	
	%	65,0%	35,0%	100,0%	
Total	n	24	15	39	
	%	61,5%	38,5%	100,0%	

Succesful hematological response was seen more in female subjects than male subjects (65% vs. 57.9% respectively), as shown in Table 4. There was no statistically significant association between gender and hematological responses achievement (p = 0.648).

Table 5. Type of Therapy And Its Conjunction with Hematological Response Achievement

Type of Therapy		Hematological Response		Total	p (C.I. 95%)
		Achieved	Not Achieved		
Hydroxy Urea	n	5	9	14	0,046
	%	35,7%	64,3%	100,0%	
Imatinib	n	6	2	8	
	%	75,0%	25,0%	100,0%	
Nilotinib	n	13	4	17	
	%	76,5%	23,5%	100,0%	
Total	N	24	15	39	
	%	61,5%	38,5%	100,0%	

Table 5 shows hydroxy urea therapy resulted in the hematological responses achievement of 5 subjects (35.7%), less than those who did not achieve hematological responses (n = 9 ; 64.3%). Imatinib therapy resulted in the hematological response achievement of 6 subjects (75%); a higher number than those who did not achieve hematological responses.(n = 2 ; 25%) Nilotinib therapy, resulted in the hematological response achievement of 13 subjects (76.5%), a higher number than those who did not achieve a hematological response(n = 4 ; 23.5%) . A significant association between types of therapy with the achievement of hematological response (p = 0.046). Nilotinib therapy resulted in the highest number of hematological response achievement, compared to Imatinib and Hydroxy Urea therapy (54,1% vs. 25.0% vs. 20.9% respectively).

Table 6. Comparison of Blast Cell Percentage In Different Hematological Response Achievement

Hematological Response	n	Mean (%)	SD	p (C.I. 95%)
Achieved	24	6,1	1,8	0,016
Not Achieved	15	7,9	2,6	

The mean of blast cell was found to be significantly lower in subjects who achieved a hematological response compared to subjects who did not (6.1% vs. 7.9% respectively, p = 0.016).

Discussion

Age: Subjects who achieved hematological response at age ≥40 years (66.7%) was higher than at age <40 years (57.1%). However, there is no statistically significant association between age and the achievement of hematological response.

Increasing age was commonly associated with CML development into an advanced stage. Research conducted by Cortes and colleagues, showed that patients treated with Imatinib achieve a better hematological response and cytogenetic response in patients under 65 years compared with those above 65 years of age, but there is no significant correlation between age and induction remission of hematology.[7] Research conducted by Safaa and colleagues in Egypt found there was no significant difference between age, gender, and social status in achieving therapeutic targets.[8]

Age is related to tolerability and poor adherence so it influences the response of therapy. Old age experiences many drugs side effects of both hematological and non-hematological compared to young age. Research by Rosti and colleagues found that old age was associated with poor prognostic factors for outcome in CML Philadelphia chromosome (+) patients.[9] Arora's study explained that age also affect drug pharmacokinetics, besides adherence, number of transporters, drug interactions and drug - plasma protein binding.[10]

Gender: In this study, there was no significant difference in the percentage distribution of hematological responses achievement between male and female, although it was seen to be higher in female (65%) than in male (57.9%) (p =0.648). No significant association was found between gender and the achievement of hematological responses.

Research by Singh and colleagues explains that the achievement of a hematological response and poor cytogenetic and prognostic responses are found in patients with older age and female gender, but do not elaborate further on the cause of this.[6]

Differences in achievement between male and female are explained as a result of poor adherence and tolerance found in male gender.[11,12] Pharmacokinetic variability also has an important role. Differences in body weight might also explain the differences in drug concentrations in male and female. Lighter weight in female mean female get an average dose of milligrams per kilogram of body weight higher than male, which means higher plasma drug concentrations.[13]

Type of Therapy: The percentage of subjects who achieved hematological response was found to be significantly higher in the administration of Nilotinib than those with Imatinib and hydroxy urea (54,1% vs. 25.0% vs. 20.9% respectively). A significant association was found between types of therapy and the hematological response achievement (p = 0.046).

The study of Safaa and colleagues in Egypt found that 71.6% and 67.2% of patients who received Gleevec (Imatinib) achieved complete hematological response and cytogenetic responses. Patients who received hydroxy urea therapy, only 34.1% and 31.9% achieved a complete therapeutic response.[8]

Research conducted by Zhao et al. In 116 early chronic phase of CML patients treated with imatinib in China, obtained a complete hematological response of 94.1% .[14]

Research by Parveen Jain et al., Which compared treatment with tyrosine kinase inhibitors in this case imatinib with hydroxy urea, obtained 95% results achieving complete hematological response compared to 30% receiving hydroxyurea.[15] In a study conducted by Druker[16], O'Brien[17], and Kantarjian[18], around 95% of patients achieved a complete hematological response. Research conducted by the Benelux CML study group, by Hehlmann and colleagues, shows that about 35% of patients achieve a complete hematological response with the use of hydroxy urea.[19]

Treatment of CML has experienced a rapid rate of progress over the past few years. Breakthroughs in the molecular targets of tyrosine kinase inhibitor (TKI) in recent years have brought changes in the history of the disease and in the therapeutic approach to patient treatment. The action mechanism of this TKI class of drugs are to selectively inhibit tyrosine kinase activity by occupying the ATP binding domain in ABL thereby preventing substrate phosphorylation.[20]

Blast Cells Percentage: The mean of blast cells was found to be significantly lower in subjects who achieved hematological response (6.1% vs. 7.9%, p = 0.016). The percentage of the number of blast cells has a prognostic factor in CML disease. The large number of blast cells circulating in the peripheral blood is also associated with the clinical phases of CML (chronic phase, acceleration, blast crisis), where the further phase, the more the number of blast cells circulating in the peripheral.

The increased blast in CML is a direct consequence of continued BCR-ABL activity, possibly through oxidative stress and reactive oxygen species, resulting in DNA damage and impaired DNA repair, and subsequently causing genetic instability and clonal evolution with additional cytogenetic aberration and multiple mutations in the kinase domain BCR-ABL.[21]

Based on this study, age and gender did not have an association with achieving hematological response. There is a significant association between type of therapy and the percentage of blast cells with achieving complete hematological response. However, further research needs to be done on other factors that might affect the achievement of hematological response in CML patients, such as medication adherence and the possibility of resistance to drug administration.

Conclusion

The type of therapy (nilotinib) and the low percentage of blast cells have an association with achieving complete hematological response.

Conflict of Interest: No Potential conflict of interest relevant to be declared

Source of Funding: This study was conducted with self funding , no external funding sources for this study

Ethical Clearance: The study protocol was approved by the Ethics Committee in Research of our instituion (Hasanuddin University), following the ethical reccomendations from the Helsinki Declaration of 1975.

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