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A Three-Years Survival Rates of Chronic Myeloid Leukemia Patients with Targeted Therapy

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Abstract

Introduction: Chronic myeloid leukemia (CML) is a hematopoietic stem cell cancer driven by the BCR-ABL fusion protein that arises from the translocation of chromosomes 9 and 22. Since the found of the Tyrosine Kinase Inhibitor (TKI) as a targeted therapy, the relative survival rate of 5 years has significantly increased compared to the era of the use of previous agents. As a successful leukemia treatment, it can be seen based on the survival rate. Several factors have been known to influence the survival and prognosis of CML patients, including the age of the patient at diagnosis, gender, and response to therapy and treatment. This study aims to determine how many a three-year survival rates for CML patients with targeted therapy in Makassar and the factors that affect survival.

Method: This study used a retrospective cohort using secondary data (medical records) of CML subjects who had been outpatient or inpatient followed in the same time period. The study was conducted in January 2015 to December 2017 at Dr. Wahidin Sudirohusodo Hospital, Makassar. The samples consisted of 108 subjects who met the inclusion criteria. Gender, age, BCR-ABL transcript, targeted therapy and status were taken from medical records. Data were analyzed with SPSS 22.0 version and survival analysis, Meier Kapplan curves, survival median, log-rank and test statistic

Results: There were 108 subjects of CML patients who received targeted therapy, 58 male (53.7%), 30-39 years old 32 subjects (29.6%), b3a2 transcript 67 subjects (73.6%), Imanitib 62 subjects (57.4%) and status for 36 months was followed during the targeted treatment of dead 19 subjects (17.6%) and alive 89 (82.4%). The survival rate of a three years CML subjects who received targeted therapy of 51%, found no significant relationship between gender, age, and targeted therapy

Conclusion: The survival rate of three years of CML patients at Wahidin Sudirohusodo Makassar Hospital is 51% and factors related to age, gender, and targeted therapy tend to influence even though statistically not significant

Keywords: *Three-year survival, CML, targeted therapy.*

Introduction

Chronic myeloid leukemia (CML) is a hematopoietic stem cell cancer driven by the BCR-ABL fusion protein that arises from the translocation of chromosomes 9 and 22.(1) The conjugation of the breakpoint cluster region (Bcr) gene on chromosome 22 and the Abelson kinase (Abl) gene on chromosome 9 creates the Bcr-Abl oncogene, which encodes the deregulation of tyrosine

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kinase. Bcr-Abl activity will create uncontrolled cell proliferation and reduce apoptosis, thereby it will increase malignant expansion of pluripotent stem cells in the bone marrow.[2,3]

Data on CML in Indonesia in 2018 obtained as many as 2,374 patients, most in Surabaya as many as 516, while at least, in Banda Aceh as many as 40, and in Makassar as many as 110. The median age for CML event is 45-55 years old and the event will increase with age.[4]

By recognizing the molecular basis of CML, a highly effective targeted therapy has been developed. This therapeutic agent will block the activity of the tyrosine kinase inhibitor (TKI) of Bcr-Abl in which will inhibit the course of the CML molecular process. Since the found of the Tyrosine Kinase Inhibitor (TKI), the relative survival rate of 5 years is much increased compared to the era of the use of the previous agent. The first generation of Tyrosine Kinase Inhibitor, Imatinib Mesylate was proven to provide excellent clinical outcomes. In Indonesia, the use of TKI has been applied to CML patients and has reached the use of the second generation namely Nilotinib (Tasigna). The comparison of the survival of the two target therapy was reported in the ENESTnd study (Evaluating Nilotinib Efficacy and Safety in Clinical Trial-Newly Diagnosed Patients) where from the 5-year follow-up of patients with nilotinib 300 mg of 93.7%; nilotinib 400 mg by 96.2% and Imatinib 400 mg by 91.7% did not show a significant difference between the two. However there were differences in death due to progression from CML, namely 16 Imatinib death 93.8% while 6 Nilotinib death 97.7%.[5] The survival of CML patients with imatinib in 2006 reported by Drukker, et al. stated an overall survival of 89% after five years.[6]

As a successful leukemia treatment, it can be seen based on the survival rate.. In leukemia patients, using a five year survival rate. This was study carried out for three years as in the second or third year the patient level of compliance sometimes begins to decrease because they felt healed. Several factors that have been known to affect the survival and prognosis of CML patients include the patient's age at diagnosis, gender, and response to therapy and treatment. Now days there is no data of survival rates of CML with targeted therapy in Makassar, therefore we are conducting this research.

Method

This study used a retrospective cohort using secondary data (medical records) of CML subjects who had been outpatient or inpatient followed in the same time period. The study was conducted in January 2015 to December 2017 at Dr. Wahidin Sudirohusodo Hospital in Makassar. Samples were CML patients who met the inclusion criteria included (1) CML patients based on BMP (2) positive BCR-Abl (3) age ≥ 18 years (4) willing to join the study. Exclusion criteria (1) Patient cannot be contacted either by telephone (2) Incomplete data. The minimum number needed is 61 research subjects. Sampling was carried out consecutively during the study period until the desired number of samples was reached. Furthermore, Data were analyzed with SPSS 22.0 version and survival analysis, Meier Kapplan curves, survival median, log-rank and test statistic.

Results

From this research, subject studied was 108 CML patients with target therapy, consisted of 58 male (53.7%) and 50 female (46.3%). Age of the subjects were 30-39 years is 32 (29.6%). Bcr-abl transcripts of the subjects is b3a2 with 67 subjects (73.6%), 22 subjects (24.2%) b2a2, and 1 subject (1.1%) c3a2 and e1a3 respectively. Subjects receiving targeted therapy were imatinib 62 subjects (57.4%) and nilotinib 46 subjects (42.6%). The last status during the administration of target therapy is dead 19 subjects (17.6%) and alive 89 (82.4%). It can be seen in table 1.

Table 1. Distribution of Sample Characteristic (n=108)

Variable		n	%
Gender	Male	58	53,7
	Female	50	46,3
Age	<30 years	24	22,2
	30-39 years	32	29,6
	40-49 years	26	24,1
	50-59 years	16	14,8
	>=60 years	10	9,3
BCR-ABL Transcript	b2a2	22	24,2
	b3a2	67	73,6
	c3a2	1	1,1
	e1a3	1	1,1
Targeted therapy	Imatinib	62	57,4
	Nilotinib	46	42,6
Status	Dead	19	17,6
	Alive	89	82,4

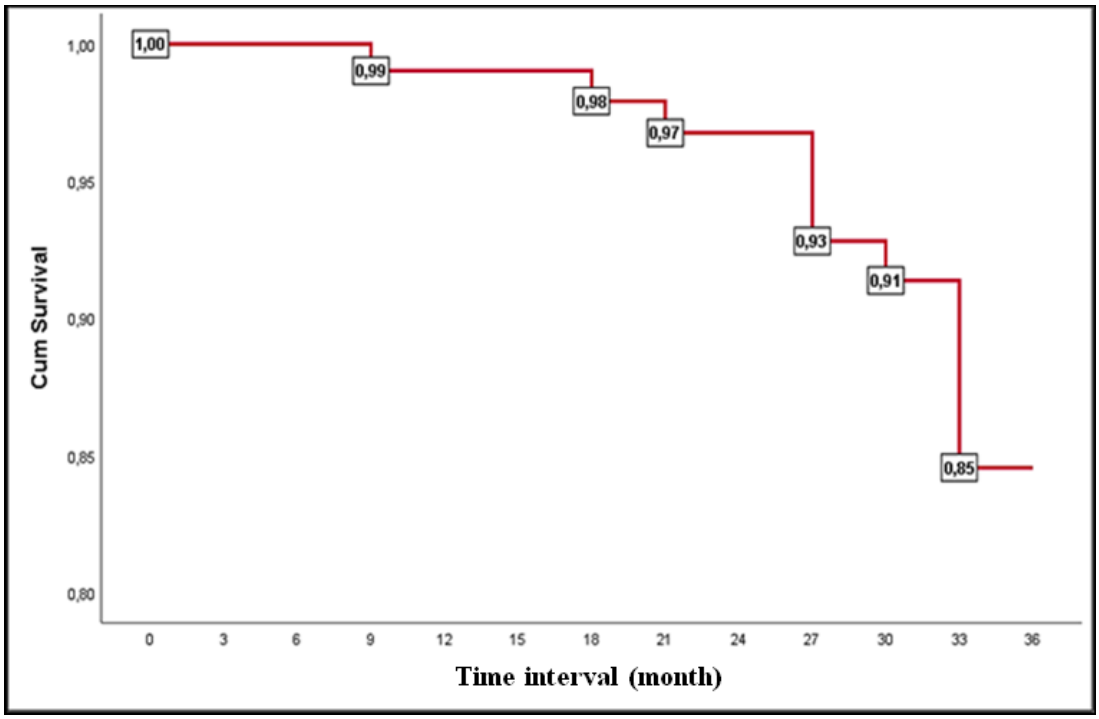

Figure 1. Kaplan-meier Curves of Three-year Survival Probability

Three-year survival rate for CML patients with targeted therapy, an analysis using the life table-Wilcoxon (Gehan) method was obtained, and a one-year survival rate (99%), a two-year survival rate (93%) and a three-year survival rate (51%) (table 2).

Table 2. A Three-Year Survival Analysis of CML Patients

Time interval (month)	n	Survival (%)
0	108	100
3	108	100
6	106	99
9	98	99
12	91	99
15	89	98
18	88	97
21	81	97
24	77	93
27	67	91
30	61	85
33	42	85
36	32	51

Figure 1 shows the probability of survival at each 3-month interval in the Kaplan-Meier curve. The duration of follow-up of all patients is from 5 to 102 months with a mean of 30.4±16.3 months.

Table 3. Three Years Survival of CML Patients by gender

Gender	n	Survival Estimation		p
		Mean (Month)	%	
Male	58	34,6	43	0,856
Female	50	34,2	57	

Table 3 shows that survival in female is higher than in male, which is 57% and 43% (34.2-34.6 month), but statistically not significant (p> 0.05).

Table 4. Three Years Survival of CML Patients by Age

Age (Years Old)	n	Survival Estimation		p
		Mean (Month)	%	
<30	24	34,5	73	0,631
30-39	32	34,9	64	
40-49	26	34,4	54	
50-59	16	34,1	37	
>=60	10	33,8	29	

Table 4 also shows a decrease with increasing age, but not statistically significant (p> 0.05). The highest survival occurred at age <30 years (73%) and the lowest was at age > = 60 years (29%).

In general, survival in the two treatment targets was not found to be statistically significant difference (p> 0.05) (table 5).

Table 5. Three Years Survival of CML Patients by Targeted Therapy

Targeted therapy	n	Survival Estimation		p
		Mean (Month)	%	
Imatinib	62	34,3	52	0,849
Nilotinib	46	34,7	47	

Table 5 also show imatinib gives the highest survival rate (52%) compared to nilotinib (47%). The mean survival rate is also not much different, namely 34.3-34.7 months.

Discussion

This study found that the subjects studied was 108 CML subjects. Most of the subjects were male: 58 (53.7%) and 50 female (46.3%). This result is in line with research conducted by Reksodiputro et. al. in 2011 in Jakarta, where 19 reported samples were studied, slightly dominant in males than females at 63.2%.[7] Several overseas studies conducted by Hofmann in 2015 reported that CML patients were more frequent in male than female.[8] Research was also supported by SEER (Surveillance, Epidemiology, and End Results) USA which stated that of all race, the ratio of male and female from CML is 2.2:1.3.[9]

Age range between 18-72 years old with an average of 39.8±13.1 years old. Research conducted by Reksodiputro et. al. in 2011 where the age of CML patients was in the age range of 13-62 years.[7] It is different from American Cancer Society data that CML cases in the United States in 2019, the average age at diagnosis of CML is around 64 years. Nearly half of the cases are diagnosed in people aged 65 and older.[10]

The duration of follow-up of all patients is from 5 to 102 months with a mean of 30.4±16.3 months. In this study, a one-year survival rate of 99%, a two-year survival rate of 93% and a three-year survival rate of 51% (table 2 and figure 1). This study carried out for three years because, in the second and third years, the patient level of adherence in treatment slowly decreased, where patients sometimes seemed to have felt healed with the disease they experienced. In a study conducted by Di Felice et. al. in 2018 in Italy, 357 subjects reported having CML after being given TKI, survivability for one year (from 83.3, 95% CI 76.2-88.5% to 91%, 95% CI 86.5-94.4%) and survival for three years (from 60.4, 95% CI 51.7- 68% to 84.5%, 95% CI 79-89%).[11]

Survival rate for female was higher at 57% and for male 43%, with a mean survival rate at 34.2-34.6 months. But it did statistically not significant (p> 0.05) (table 3). Research by Berger et. al. in 2005 in Germany reported 856 subjects with Ph/BCR-ABL-positive CML in a randomized CML study, where the survival rate was average longer in female sufferers than in male with an average of 59-49 months and this also not significance.[12]

It is well known that age is a very important prognostic marker, and old age has several times been associated with poor survival. In this study, survival analysis according to age was found to be highest at age <30 years old (73%) and lowest at age> = 60 years old (29%).The decrease occurred with increasing age, but it was not statistically significant (p> 0.05) (table 4). Research by Castagnetti F et. al. in 2017 in Italy reported 337 CML patients, obtained OS was not affected by age in the interval between 18-69 years old (OS 5 years 92%, average from 89% to 95% in different decades), but the probability of OS 5 years for old age (≥ 80 years) was significantly lower (34%, P <0.0001).[13] Research by Di Felice et. al. in 2018 in Italy, reported survival by age was relatively decreased, age <65 years old (from 69%, 95% CI 55.3-79.5% to 94%, 95% CI 88.4-97.4%), age 65-74 years old (from 46%, 95% CI 30.8 -61.2% to 69%, 95% CI 52.5-80.4%) and age> 74 years old (from 8.05%, 95% CI 0.8-26.7% to 51, 2%, 95% CI 32.4-67.1%).[11] It can be assumed that relatively older ages have poor survival.

In general, the survival the Imatinib and Nilotinib, was not found to be statistically significant (p> 0.05). Imatinib highest survival rate (52%) compared to nilotinib (47%) with the mean survival rate also not much different, ie 34.3-34.7 months (table 5). The Food and Drug Administration (FDA) approved imatinib as the first-line treatment for newly diagnosed CML in December 2002 after the International Randomized Study (IRIS), which began in June 2000, the results of this study show the effectiveness of imatinib and its remarkable superiority with respect to complete haematological response rates (CHR), molekuler and complete cytogenetic responses

(MCyR, CCyR) with an overall survival rate (OS) of 85% for patients receiving imatinib.[13] This is different from the ENESTnd study by Larson et. al. (2012) in the United States, which examined 868 subjects comparing nilotinib (300 mg and 400 mg doses respectively) with imatinib, estimated that the three-year survival rate was higher in nilotinib with imatinib is nilotinib 300 mg 95.1%, nilotinib 400 mg 97.0% and 94.0% for imatinib. [14] While another study by Sanglio et. al. (2010) in Australia also found that nilotinib at a dose of 300 mg or 400 mg twice daily was better than imatinib in CML patients with newly diagnosed positive Philadelphia chromosomes.[15] According to Au WY et. al. (2009), In general, Asian patients, the use of imatinib is still used as the first choice therapy for treating CML patients. Either from Asia, Europe or the United States for giving imatinib is generally giving a good response. Most health practitioners in Asia follow the guidelines found on ELN (European Leukemia Net) or NCCN (National Comprehensive Cancer Network). Based on the results of studies that have been collected regarding the response of CML patients to imatinib, in Europe and the United States shows a complete hematological response of more than 95%, while in Thailand, Philippines, India, China, Hong Kong and South Korea by 90-100%.[16]

This study carried out no dose distribution of nilotinib or imatinib and no further examination of the molecular response achieved which should be examined every year after administration of target therapy so that the results found were inadequate. Besides, various factors influencing the survival of the comparison between the two target therapy are not evaluated precisely such as adherence to take medication or how to take medication, cause of death and the presence or absence of a previous comorbid patient history.

Conclusion

Survival rate of three years of CML patients at Wahidin Sudirohusodo Hospital in Makassar was 51% and factors related to age, gender, and target therapy tended to influence even though it was not statistically significant.

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

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Ethics Committee: It has been approved by the ethical committee of Hasanuddin University Faculty of Medicine with reference number: 429/UN4.6.4.5.31/ PP36-KOMETIK/2019.

References

1. Faderl S, Talpaz M, Estrov Z, et al.. Chronic myelogenous leukemia : Biology and therapy. Ann Intern Med. 1999;131:207-219
2. Branford S, Rudzki Z, Hughes TP . A novel BCR-ABL transcript (e8a2) with the insertion of an inverted sequence of ABL intron 1b in a patient with Philadelphia-positive chronic myeloid leukaemia. Br J Haematol.2000; 109: 635-637.
3. Yuan H, Wang Z, Gao C, Chen W, Huang Q, et al. BCR-ABL gene expression is required for its mutations in a novel KCL-22 cell culture model for acquired resistance of chronic myelogenous leukemia. J Biol Chem.2010; 285: 5085-5096.
4. Reksodiputro, Arry Harryanto., Atmakusuma, et al. Chronic Myeloid Leukemia in Indonesia. 2018. Dharmais Hospital National Cancer Centre. DOI: 10.13140/RG.2.2.18070.24644
5. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016; 30(5):1044-1054
6. Druker BJ, Guihot F, O'Brien SG, et al. Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia. N Engl J Med. 2006; 355:2408-2417
7. Reksodiputro A H, Tadjoedin H, Rinaldi I.. Clinical Characteristic, Hematologic Response and Gene Mutation of Patients with Chronic Phase Chronic Myeloid Leukemia (CML) to Imatinib at Cipto Mangunkusumo National Hospital (RSUPN CM). Depok: Indonesian Journal of Cancer. 2011; 5(4):419
8. Hofmann VS, Baccarani M, Hasford J, et al. THE EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 european countries. Leukemia. 2015; 29(6):1336-1343
9. Anonim. Surveillance, Epidemiology, and End Results Program Stat Fact Sheets: Leukemia. [Online] Tersedia di: http://seer.cancer.gov/ statfacts/html/leuks.html diakses pada 18 September 2015

10. American Cancer Society. Cancer Facts & Figures. Atlanta. 2019
11. Di Felice enza, Francesca Roncaglia, Francesco Venturelli, et al.. The impact of introducing tyrosine kinase inhibitors on chronic myeloid leukemia survival: a population-based study. BMC Cancer. 2018;18:1069
12. Berger, O Maywald, M Pfirrmann. Gender aspects in chronic myeloid leukemia: long-term results from randomized studies. Leukemia.2005;19; 984-989
13. Castagnetti F, Di Raimondo F, De Vivo A, et al. A population-based study of chronic myeloid leukemia patients treated with imatinib in first line. Am J Hematol. 2017; 92:82-87
14. Larson RA, Hochhaus A, Hughes TP,et al.. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phasen : ENESTnd 3-year follow-up. Leukemia. 2012; 1-7
15. Sanglio G, DW kim, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med.2010 Jun 17; 362(24):2251-2259
16. Au WY, Caguioa PB, Chuah C et al. Chronic Myeloid Leukemia in Asia. Int J Hematol Springer. 2009; 89:14-23