RESEARCH ARTICLE

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Long-Term Outcomes with Sequential Tyrosine Kinase Inhibitors Treatment in Chronic Myeloid Leukemia Patients

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Abstract

Objective: Tyrosine kinase inhibitor (TKI) is the standard treatment for chronic myeloid leukemia (CML). In the national list of essential medicines in Thailand, the first, second, and third-line treatments are imatinib, nilotinib, and dasatinib, sequentially, different from the European Leukemia Net guidelines. This study aimed to evaluate the outcomes of CML patients who received sequential treatment with TKI. **Methods:** This study enrolled CML patients diagnosed between 2008 and 2020 at Chiang Mai University Hospital who received TKI. Medical records were reviewed for demographic data, risk score, treatment response, event-free survival (EFS), and overall survival (OS). **Result:** One hundred and fifty patients were included in the study, 68 patients (45.3%) were female. The mean age is 45.9 ± 15.8 years. Most patients (88.6%) had good ECOG status (0-1). The CML diagnosis was in the chronic phase in 136 patients (90.6%). The EUTOS long-term survival (ELTS) score revealed a high of 36.7%. At the median follow-up of 8.3 years, 88.6% of patients were in complete cytogenetic response (CCyR), whereas 58.0% were in major molecular response (MMR). The 10-year OS and EFS were 81.33% and 79.33%, respectively. The factors associated with poor OS were high ELTS score ($P = 0.01$), poor ECOG performance status ($P < 0.001$), not achieved MMR within 15 months ($P = 0.014$), and not achieved CCyR within 12 months ($P < 0.001$). **Conclusion:** The sequential treatment for CML patients had a good response. Factors predicting survival were ELTS score, ECOG performance status, and early achieving MMR and CCyR.

Keywords: CML- TKI- imatinib- nilotinib- dasatinib

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Introduction

Chronicmyeloid leukemia (CML) is a myeloproliferative neoplasm marked by active BCR-ABL tyrosine kinase, which is derived from reciprocal translocation of t(9;22)(q34;q11) or the presence of Philadelphia (Ph) chromosome (Cumbo et al., 2020). Arsenic, irradiation, alkylating agents, and hydroxyurea have all been used to treat CML in the past. However, none of these treatments proved to be successful in the end. The mortality rate remains high (Woessner et al., 2011). Basic science has defined the molecular pathogenesis of CML as unregulated signal transduction by a tyrosine kinase. In 1998, since the pathogenesis of CML was well-established, the introduction of tyrosine kinase inhibitor to be the main treatment of CML has revolutionized management among CML patients (Hochhaus, 2003). Currently, the main treatment of CML is tyrosine kinase inhibitors (TKIs) including imatinib (first-generation TKI), nilotinib, dasatinib, and bosutinib (second-generation TKIs) (Cuellar et al., 2018). Several TKIs are approved for CML treatment determined by consideration of efficacy, toxicity, and drug costs. According to European Leukemia Net (ELN), each imatinib, nilotinib or dasatinib is recommended as front-line therapy. Other TKIs could be used as a second or third-line treatment, depending on the patient's risk score (Sokal score) (Aijaz et al., 2020) and EUTOS long-term survival (ELTS) score) (Pfirrmann et al., 2016), mutation of BCR-ABL tyrosine kinase and comorbidities (Baccarani et al., 2013; Hochhaus et al., 2020).

However, the first-line treatment of CML in Thailand is imatinib according to the national list of essential medicine of the country, which considered the cost-effectiveness of the drug. Sequential treatment was recommended with nilotinib and dasatinib for the second and third-line

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therapies, respectively. The therapy options available in Thailand are different from those indicated by the ELN guidelines.

The objective of this study was to assess long-term outcomes (overall survival and event-free survival) in CML patients who were sequentially treated with imatinib, nilotinib, and dasatinib as first, second, and third-line treatments, respectively.

Materials and Methods

Study Design

This study is a retrospective study enrolled CML patients in Chiang Mai University Hospital. The study was carried out with the approval of the Institutional Review Board. (Study number: MED-2563-07233/Research ID 7233).

Study Population

Eligible patients had to be at least 15 years of age and diagnosed with CML between January 2008 - March 2020. The diagnosis was confirmed by the identification of the Philadelphia chromosome by conventional cytogenetic method and/or molecular method for detection of BCR – ABL1 fusion gene by fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR).

Medical records were examined for demographic information, comorbidities, CML risk scores (Sokal and ELTS), treatment response milestones (based on ELN guidelines), events, and deaths. Assessments of the patient's overall prognosis were made with the use of the scoring system including Sokal and ELTS score.

Response Evaluation

The surrogate markers used to evaluate treatment response were cytogenetic and molecular responses. The response to TKI is an important prognostic factor. Treatment response was defined as optimal, warning, or failure according to ELN guideline 2013 (Baccarani et al., 2013) (Supplementary Appendix Table 1,2). Patients with optimal response continued the current treatment, whereas patients with failure were switched to a later line of TKIs.

Endpoints

The evaluation of therapeutic efficacy should be based on overall survival (OS) and event-free survival (EFS). The composite primary outcomes were EFS and OS. EFS was defined as survival without, loss of complete hematologic response (CHR), loss of major molecular response (MMR), progression to accelerated phase (AP) or blastic phase (BP), and death from any cause during treatment. OS was defined as the time from diagnosis to death from any cause. The survival status was explored from the medical records and confirmed with the Thai National database (Official statistics registration systems). In case that the 30 patients had died, date of death, causes of death was collected. Secondary outcomes included response at 3, 6 and 12 months according to response milestones from ELN recommendations for the management of chronic myeloid leukemia 2013, prognostic factors related to response, EFS, OS, and CML-related death (death due to progression of the disease).

Statistical Analysis

According to the previous study; the long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia, respectively and estimated six-year overall survival (OS) rates were 71% from 724 patients (Shah et al., 2014). With a difference of 10% from that overall survival rate, this study required sample size of at least 149 patients with a 95% confidence interval and 80% power of the test.

Demographic data were shown as a number with percentage or mean with standard deviation. Categorical data were compared by Chi-square test or Fisher's Exact test. Continuous data were analyzed by the Student t-test. For OS and EFS analyses, the Kaplan-Meier curve was calculated.

95% confidence interval was calculated in all associations and a two-sided P value less than 0.05 was considered statistically significant. Univariable and multivariable Cox proportional hazards models were used to explore factors that influence primary outcomes. For the multivariable approach, stepwise inclusion of predictors was utilized to generate the model. All univariate analytic comparisons of clinical variables with a P value of less than 0.05 for OS, EFS, and CML-related death were included in the model. Data were analyzed using the Stata Statistic Software version16 (StataCorp LLC, USA).

Results

Baseline Characteristics

All 150 patients who were diagnosed with CML between January 2008 - March 2020, were enrolled in the study. All patients received imatinib as a first-line treatment. Fifty-six patients received first and second line as imatinib and nilotinib. Twenty patients were given all three TKIs as first, second, and third lines, respectively.

Baseline characteristics are listed in the Table 1. Sixty-eight patients (45.3%) were female. The mean age at diagnosis was 45.9 years (SD 15.8 years). Most of the patients (88.37%) had good ECOG performance status (ECOG 0-1). The phase of CML diagnosis included chronic phase 136 patients (90.6%), AP eight patients (5.3%) and BP six patients (4%). The ELTS score revealed low at 35.3%, intermediate at 28.0%, and high at 36.7%. On the other hand, Sokal's score revealed 4%, 40%, and 56% for low, intermediate, and high risk, respectively.

Response milestone

Optimal response at 3, 6 and 12 months after first-line imatinib were 98 (65.33%), 75 (50%) and 70 (46.67%) patients. Of 56 patients, (53 patients failed imatinib and the remaining had intolerance) received second-line treatment as nilotinib, optimal responses in 3, 6, and 12 months were 43 (76.79%), 41 (73.21%), and 39 (69.64%) patients. Among 20 patients who received all three TKIs, 17 patients failed and three patients had an intolerance to nilotinib treatment. Of those six (30%), five (25%), and five (25%), respectively had optimal results in three, six,

Table 1. Baseline Characteristics of CML patients with Sequential Tyrosine Kinase Inhibitors Treatment in Thailand from 2008 to 2020

Variables	Total (N=150) (%)
Sex	
Female	68 (45.33)
Male	82 (54.67)
Age	54.34 ± 16.48
Age of Diagnosis	45.99 ± 15.77
ECOG Performance Status Scale	
0 – 1	133 (88.67)
2 – 4	17 (11.33)
Underlying Disease	56 (37.33)
Diabetes Mellitus	7 (12.50)
Hypertension	19 (33.93)
Dyslipidemia	12 (21.43)
Chronic kidney disease	4 (7.14)
Coronary artery disease	2 (3.57)
Cerebrovascular disease	5 (8.93)
Other	38 (67.86)
CML Phase	
Chronic	136 (90.67)
Accelerated	8 (5.33)
Blastic	6 (4)
Ph Chromosome study method	
Cytogenetic study	149 (99.33)
FISH	1 (0.67)
Sokal score	
Low	6 (4)
·Intermediate	60 (40)
High	84 (56)
ELTS score	
Low	53 (35.33)
Intermediate	42 (28)
High	55 (36.67)

and 12 months (Figure 1).

Progression and Survival

The 30 patients (20.0%) were death and CML-related death had 13 patients (8.7%). At the median follow-up of 8.3 years, 88.6% of patients were in complete cytogenetic response (CCyR), whereas 58.0% were in major molecular response (MMR). The estimated overall survival (OS) rate at ten years is 81.33% (Figures 2a) and ten years of event-free survival (EFS) is 79.33% (Figures 3a). Median OS and EFS were not reached. Kaplan-Meier estimates of overall survival in CML patients stratify by ECOG score (Figure 2b), stratify by ELTS score (Figure 2c), stratify by time to CCyR (Figure 2d), respectively. Kaplan-Meier estimates of event-free survival in CML patients stratify by ECOG score (Figure 3b), stratify by ELTS score (Figure 3c), stratify by time to CCyR (Figure 3d), respectively.

Prognostic Factors

Based on univariable analyses, factors that were reported to be associated with poor OS were poor ECOG performance status (ECOG2-4) (Hazard ratio (HR) 4.65, 95% CI 2.23-9.71, P<0.001), not achieved MMR within 15 months (HR 2.49, 95% CI 1.20-5.15, P = 0.014), not achieved CCyR within 12 months (HR 4.56, 95% CI 2.02-10.28, P<0.001), high ELTS score (HR 3.79, 95% CI 1.38-10.46, P = 0.01), high Sokal score was also associated with the poor OS but not achieved statistically significant (HR 2.33, 95% CI 0.31-17.3, P = 0.408) (Table 2).

Furthermore, poor ECOG performance status and high ELTS score were also associated with poor EFS (HR 5.51, 95% CI 2.70-11.22, P < 0.001 and HR 2.54, 95% CI 1.04-6.25, P 0.042, respectively). Following OS, failure to attain MMR within 15 months and failure to reach CCyR within 12 months were associated with poor EFS (HR 2.84, 95% CI 1.39-5.78, P = 0.004 and HR 5.50, 95% CI 2.45-12.3 Tables 2 and 3 also show the results of multivariable analyses that included variable factors that influenced OS and EFS. Poor OS was associated with a poor ECOG performance status (HR 3.32, 95% CI 1.56-

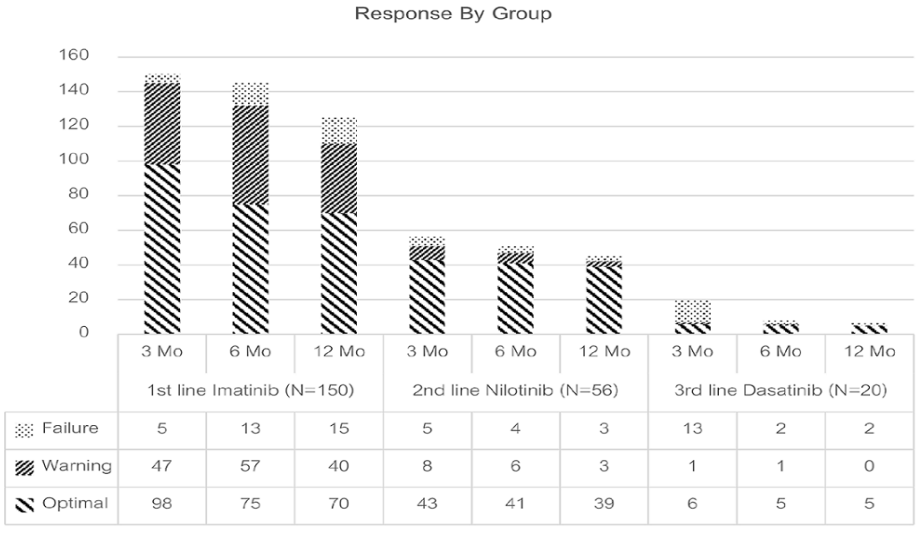

Figure 1. Response after TKIs Treatment.

Table 2. Risk Factors of OS in CML Patients

Variables	Total	Death	95% CI	Log-rank test	Univariable Analyses			Multivariable Analyses		
	(N=150) (%)	(N=30) (%)		(p-value)	HR	95%CI	p-value	HR	95%CI	p-value
Sex				0.164						
Female	68 (45.33)	17 (56.67)	2.20 - 5.69		Ref.					
Male	82 (54.67)	13 (43.33)	1.29 - 3.81		0.6	0.29 - 1.24	0.169			
Age	54.34±16.47	67.27±18.04	1.96 - 4.02		1.05	1.02 - 1.07	0.000	0.95	0.81 - 1.11	0.487
Age of Diagnosis	45.99±15.77	56.30±17.86	1.96 - 4.02		1.05	1.02 - 1.07	0.000	1.07	0.91 - 1.26	
ECOG				0.000						
ECOG 0 - 1	133 (88.67)	18 (60.00)	1.21 - 3.04		Ref.			Ref.		
ECOG 2 - 4	17 (11.33)	12 (40.00)	5.30 - 16.44		4.65	2.23 - 9.71	0.000	3.32	1.56 - 7.10	0.002
Underlying Disease				0.991						
No	94 (62.67)	18 (60.00)	1.74 - 4.39		Ref.					
Yes	56 (37.33)	12 (40.00)	1.63 - 5.07		1.00	0.48 - 2.07	0.991			
Diabetes Mellitus	7 (12.50)	1 (3.33)	0.22 - 11.01	0.503	0.51	0.07 - 3.76	0.511			
Hypertension	19 (33.93)	6 (20.00)	2.06 - 10.18	0.172	1.85	0.75 - 4.53	0.179			
Dyslipidemia	12 (21.43)	3 (10.00)	1.13 - 10.83	0.733	1.23	0.37 - 4.06	0.734			
Chronic kidney disease	4 (7.14)	1 (3.33)	0.33 - 16.67	0.777	0.75	0.10 - 5.52	0.778			
Coronary artery disease	2 (3.57)	1 (3.33)	0.70 - 35.05	0.714	1.45	0.20 - 10.68	0.715			
Cerebrovascular disease	5 (8.93)	4 (13.33)	3.83 - 27.22	0.003	4.37	1.52 - 12.55	0.006	2.74	0.86 - 8.80	0.089
CML Phase				0.385						
Chronic	136 (90.67)	27 (90.00)	1.91 - 4.06							
Accelerated	8 (5.33)	3 (10.00)	1.58 - 15.21		1.79	0.54 - 5.91	0.338			
Blast	6 (4)	0 (0)	-		-	-	-			
Sokal score				0.233						
·Low	6 (4)	1 (3.33)	0.24 - 12.01		Ref.					
Intermediate	60 (40)	8 (26.67)	0.94 - 3.74		1.23	0.15 - 9.85	0.845			
High	84 (56)	21 (70.00)	2.35 - 5.54		2.33	0.31 - 17.38	0.408			
ELTS score				0.024						
Low	53 (35.33)	5 (16.67)	0.51 - 2.95		Ref.			Ref.		
Intermediate	42 (28)	10 (33.33)	1.72 - 5.95		2.63	0.90 - 7.71	0.077	2.47	0.84 - 7.27	0.1
High	55 (36.67)	15 (50.00)	2.60 - 7.14		3.79	1.38 - 10.46	0.01	3.38	1.22 - 9.33	0.019
Treat				0						
1st line Imatinib	94 (62.67)	10 (33.33)	0.79 - 2.72		Ref.					
2nd line Nilotinib	36 (24.00)	8 (26.67)	1.50 - 5.98		2.15	0.85 - 5.45	0.107			
Time to MMR				0.011						
≤ 15 months	88 (58.67)	13 (43.33)	0.01 - 0.33		Ref.			Ref.		
> 15 months	62 (41.33)	17 (56.67)	0.03 - 0.07		2.49	1.20 - 5.15	0.014	1.00	0.40 - 2.51	0.993
Times to CCyR				0.001						
≤ 12 months	88 (58.67)	8 (26.67)	0.61 - 2.45		Ref.			Ref.		
> 12 months	62 (41.33)	22 (73.33)	3.48 - 8.03		4.56	2.02 - 10.28	0..000	3.62	1.58 - 8.29	0.002

7.10, P = 0.002), a high ELTS score (HR 3.38, 95% CI 1.22-9.33, P = 0.019), and not achieving CCyR within 12 months (HR 3.62, 95% CI 1.58-8.29, P = 0.002). On the other hand, poor EFS was associated with two factors including a high ECOG score (HR 4.33, 95% CI 2.08-9.01, P < 0.001) and failure to achieve CCyR within 12 months (HR 4.67 95% CI 2.05-10.52, P < 0.001).

Furthermore, CML-related death was related to high ECOG performance status (HR 5.16, 95% CI 1.66-15.97, P = 0.004) and not achieved MMR within 15 months (HR 6.32, 95% CI 1.71-23.29, P = 0.006). ECOG performance status and early MMR attainment were two indicators that independently predicted a high CML-related death rate according to multivariable analyses (HR 4.69, 95% CI 1.48-14.87, P = 0.009 and HR 6.00, 95% CI 1.60-22.48, P = 0.008) (Supplementary Appendix Table 3).

The significantly associated factor for achieving MMR and CCyR was shown in Supplementary Appendix, Tables 4 and 5. The only significant factor associated with a lower rate of MMR and CCyR was poor ECOG performance

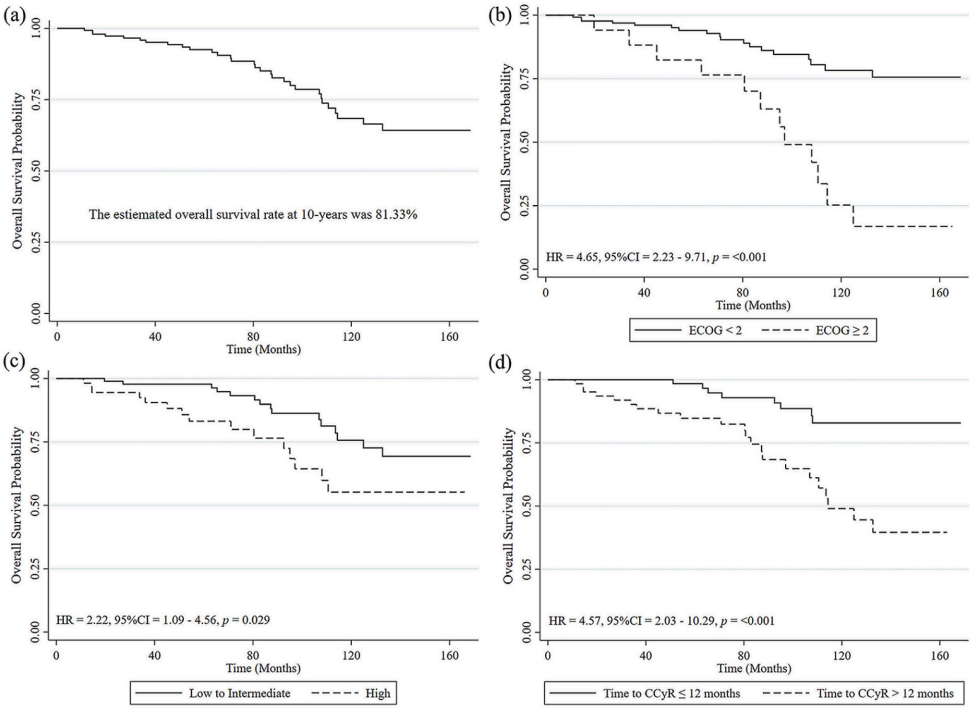

Figure 2. Kaplan-Meier Estimates of Overall Survival in CML Patients (a) Overall Survival; (b) Stratify by ECOG Score; (c) Stratify by ELTS Score; (d) Stratify by Time to CCyR.

status (HR 0.30, 95% CI 0.11-0.81, P = 0.018 and HR 0.45, 95% CI 0.25-0.80, P = 0.007, respectively).1, P < 0.001, respectively).

Discussion

The treatment of choice for CML is TKIs. According to the recommendations of the ELN, CML patients should receive treatment with a TKI. Even though the availability and the coverage by health insurance of all TKIs could vary in any country. We enrolled CML patients who underwent sequential TKI treatment (imatinib, nilotinib, and dasatinib as first, second, and third-line therapy, respectively) in this retrospective analysis to assess

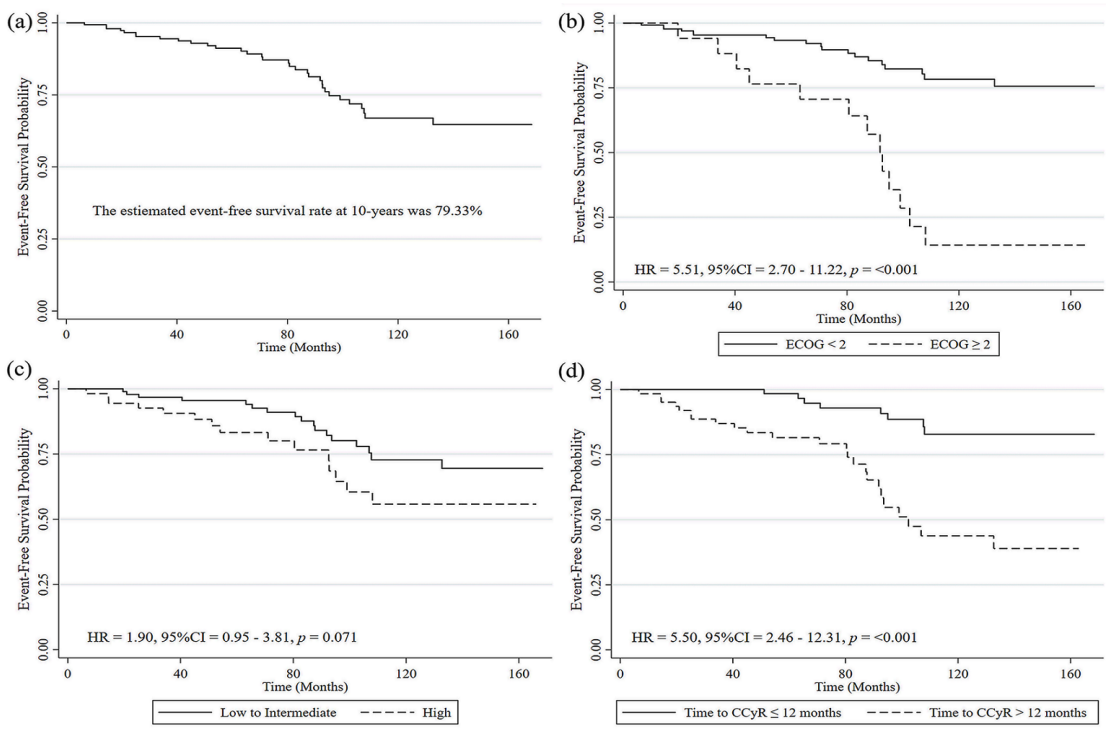

Figure 3. Kaplan-Meier Estimates of Event-free Survival in CML Patients (a) Event-free Survival; (b) Stratify by ECOG Score; (c) Stratify by ELTS Score; (d) Stratify by Time to CCyR.

Table 3. Risk Factors of Event (EFS) in CML Patients

Variables	Total	Event	95% CI	Log-rank test	Univariable Analyses			Multivariable Analyses		
	(N=150) (%)	(N=32) (%)		(p-value)	HR	95%CI	p-value	HR	95%CI	p-value
Sex				0.272						
Female	68 (45.33)	17 (53.13)	2.23 - 5.77		Ref.					
Male	82 (54.67)	15 (46.88)	1.56 - 4.30		0.68	0.34 - 1.36	0.276			
Age	54.34±16.47	66.78±17.63	2.15 - 4.30		1.04	1.02 - 1.07	<0.001	0.93	0.81 - 1.08	0.362
Age of Diagnosis	45.99±15.77	56.06±17.32	2.15 - 4.30		1.05	1.02 - 1.07	<0.001	1.09	0.93 - 1.27	0.294
ECOG				<0.001						
ECOG 0 - 1	133 (88.67)	19 (59.38)	1.30 - 3.19		Ref.			Ref.		
ECOG 2 - 4	17 (11.33)	13 (40.63)	6.42 - 19.04		5.51	2.70 - 11.22	<0.001	4.33	2.08 - 9.01	<0.001
Underlying Disease				0.76						
No	94 (62.67)	20 (62.50)	2.03 - 4.88		Ref.					
·Yes	56 (37.33)	12 (37.50)	1.64 - 5.08		0.89	0.43 - 1.83	0.759			
Diabetes Mellitus	7 (12.50)	1 (3.13)	0.22 - 11.01	0.462	0.48	0.65 - 3.53	0.472			
Hypertension	19 (33.93)	6 (18.75)	2.05 - 10.18	0.253	1.67	0.69 - 4.06	0.258			
Dyslipidemia	12 (21.43)	3 (9.38)	1.12 - 10.83	0.83	1.14	0.35 - 3.75	0.828			
Chronic kidney disease	4 (7.14)	1 (3.13)	0.33 - 16.67	0.722	0.7	0.09 - 5.12	0.723			
Coronary artery disease	2 (3.57)	1 (3.13)	0.70 - 35.05	0.802	1.29	0.18 - 9.49	0.25			
Cerebrovascular disease	5 (8.93)	4 (12.50)	3.83 - 27.22	0.007	3.82	1.34 - 10.92	0.012	2.27	0.71 - 7.23	0.167
CML Phase				0.42						
Chronic	136 (90.67)	29 (90.63)	2.11 - 4.37		Ref.					
Accelerated	8 (5.33)	3 (9.38)	1.60 - 15.40		1.67	0.50 - 5.46	0.4			
Blast	6 (4)	0 (0)	-		-	-	-			
Sokal score				0.27						
Low	6 (4)	1 (3.13)	0.25 - 12.36		Ref.					
Intermediate	60 (40)	9 (28.13)	1.10 - 4.07		1.28	0.16 - 10.13	0.82			
High	84 (56)	22 (68.75)	2.54 - 5.87		2.28	0.30 - 16.94	0.42			
ELTS score				0.11						
Low	53 (35.33)	7 (21.88)	0.84 - 3.71		Ref.					
Intermediate	42 (28)	10 (31.25)	1.73 - 5.97		1.75	0.67 - 4.62	0.25			
High	55 (36.67)	15 (46.88)	2.61 - 7.20		2.54	1.04 - 6.25	0.042			
Treat				<0.001						
1st line Imatinib	94 (62.67)	10 (31.25)	0.79 - 2.72		Ref.					
2nd line Nilotinib	36 (24.00)	9 (28.13)	176 - 6.52		2.46	1.00 - 6.09	0.05			
Time to MMR				0.028						
≤ 15 months	88 (58.67)	13 (40.63)	1.13 - 3.36		Ref.			Ref.		
> 15 months	62 (41.33)	19 (59.38)	3.14 - 7.72		2.84	1.39 - 5.78	0.004	1.13	0.46 - 2.77	0.782
Times to CCyR				<0.001						
≤ 12 months	88 (58.67)	8 (25)	061 - 2.45		Ref.			Ref.		
> 12 months	62 (41.33)	24 (75)	4.02 - 8.96		5.5	2.45 - 12.31	<0.001	4.67	2.05 - 10.62	<0.001

long-term clinical outcomes including OS and EFS.

A previous study was performed on CML patients at Chiang Mai University in 2016 (Tantiworawit et al., 2016). One hundred and twenty-three patients were included, with 57.7% of them being male and an average age of 46.9 years, and 41.5% having high Sokal scores. In this study, we reviewed all CML patients in 2021, with 54.67% male, and a mean age diagnosis of 45.9 years. A high Sokal score was noted in 56%. When comparing baseline characteristics among CML patients at Chiang Mai University at different time points, the results were in accordance.

The rate of MMR and CCyR in our study (58% and 88.6%) at the median follow-up duration of 8.3 years was comparable with the previous study. The rate of CCyR at 11 years was 82.8% in the long-term outcome of imatinib as frontline therapy in CML patients (Hochhaus et al., 2017). In the ENESTnd study, with ten years of follow-up in CML patients who were randomized to receive nilotinib or imatinib as first-line therapy, the imatinib frontline

therapy arm had an MMR rate of 62.5% (Kantarjian et al., 2021). The MMR rate in the DASISION study, which compared dasatinib to imatinib in CML patients, was 64% at five years in the imatinib group (Cortes et al., 2016).

However, the study of the second generation (dasatinib and nilotinib) as a frontline therapy showed a higher rate of CCyR and MMR. The rate of CCyR and MMR with dasatinib was 92.6% and 88.2% with a median follow-up of 6.5 years. The rate of MMR was 77.7% and 79.7% in nilotinib 300 mg and 400 mg twice daily, respectively in the ENESTnd study. The results were in accordance as the second generation TKI had a higher rate of CCyR and MMR compared to imatinib (Cortes et al., 2016; Kantarjian et al., 2021).

The estimated OS and EFS rate at ten years with sequential TKI treatment in our study was 81.33% and 79.33%. The survival rate of our study is quite comparable with the previous study with the imatinib as a frontline (IRIS study) which showed the OS rate at 83.3% (Hochhaus et al., 2017) and another study with frontline imatinib which showed the 10 year OS at 82% (Hehlmann et al., 2017). The previous study with nilotinib and dasatinib as second-line therapy after imatinib treatment also reported a long-term OS between 77-78% which was following our study (Giles et al., 2013; Shah et al., 2014; Mjali et al., 2022).

However, the treatment and outcomes of 2,904 CML patients from the EUTOS population-based registry, showed the probabilities of OS for CML patients at 12, 24 and 30 months were 97%, 94%, and 92%. The higher survival rate might be explained by this study included only CML patients with CP, and excluded AP and BP. In addition, the majority of the patients had low ELTS scores (54%). Moreover, the second generation was also used as frontline therapy. Our study populations had all stages of CML, and high ELTS scores, and all patients had imatinib as a frontline therapy (Hoffmann et al., 2017). The imatinib had lower cost of treatment compared to the second generation (nilotinib and dasatinib).

Nowadays, the generic imatinib also become available with lower cost and comparable efficacy (Eskazan et al., 2014). The frontline use of imatinib would have more cost effectiveness with acceptable efficacy. However, the second generation therapy might consider frontline therapy in high risk patient or subsequently treatment in patient with imatinib resistant mutation (Maqsood et al., 2021; Sarma et al., 2023). Furthermore, the introduction of TKIs significantly improved the survival of CML patients in our country. When compared with the previous report before the TKIs era, the overall median survival time was only 30 months. In this study, the median OS was not reached. Our study confirmed that imatinib has changed the outcome of CML patients from fatal disease to chronic manageable disease with excellent outcomes (Kim et al., 2010).

The significant associated factors with poor OS in this study were poor performance status, a high ELTS score, not achieving MMR 15 months, and not achieving CCyR within 12 months. Different clinical prognostic scores were used in clinical practice. These were including Sokal, Hasford, EUTOS, and ELTS scores. However, the Sokal and ELTS scores were recommended for use in clinical practice in the current ELN2020 and NCCN 2021 guidelines (Deininger et al., 2020; Hochhaus et al., 2020).

The recent ELTS score can predict a variety of clinical outcomes, especially in the TKI era. In the study 342 CML patients in the chronic phase were treated with any TKI as first-line therapy. The ELTS score exhibited the best accuracy in predicting patient prognosis, therapeutic responses, molecular response, OS, EFS, and CML-related death (Sato et al., 2020). This is also in agreement with our study, ELTS score was associated with OS as well as EFS. This score can be used to forecast the rate of death in TKI-treated patients. The early achievement in CCyR and MMR was associated with better OS and EFS in the previous report. The prognostic relevance of an early successful response based on an ELN milestone gives useful information for predicting positive clinical outcomes (Jain et al., 2013).

Interestingly, our study showed that poor ECOG performance status was associated with all clinical outcomes including OS, EFS, CML-related death, MMR, and CCyR achievement.

The limitations of our study were the retrospective cohort analysis that some data may be missing such as TKI-related safety and adverse events. Moreover, the findings were limited to a single center, which may limit their generalizability. However, this is the cohort of sequential tyrosine kinase inhibitors treatment in chronic myeloid leukemia patients. All patients were treated systematically with strict guidelines with long-term follow-up.

Author Contribution Statement

S.T. designed the research, collected, summarized, analyzed clinical data and wrote the paper; A.T. designed the research, collect and analyzed data, wrote the paper, gave critical comment and is the corresponding author; T.P., N.H., P.P., T.R., S.H., C.C., E.R., L.N., wrote, approved the final version for publication and gave critical comment. "All authors read and approved the final manuscript."

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General

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Approval

The study was carried out with the approval of the Institutional Review Board. (Study number: MED-2563-07233/Research ID 7233)

Ethical Declaration

The study was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University, study code No. MED-2563-07233 and performed following

guidance from the declaration of Helsinki. This study was not supported by any sponsor.

Data Availability

The data that support the findings of this study are available from the corresponding author, A.T., adisak.tan@cmu.ac.th upon reasonable request. The data are not publicly available due to privacy or ethical restrictions

Conflict of Interest

The authors declare that there is no conflict of interest.

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