SURVIVAL RATE AND PROGNOSTIC FACTORS OF SURVIVAL AMONG CHRONIC MYELOID LEUKAEMIA ADULTS AFTER INITIATION OF TYROSINE KINASE INHIBITOR THERAPY IN HOSPITAL AMPANG, SELANGOR

ZAKIAH BINTI BAKAR ALI

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by

ZAKIAH BINTI BAKAR ALI

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LIST OF SYMBOLS

<	less than
>	more than
≤	less than or equal to
≥	more than or equal to
=	equal to
+	plus
±	plus or minus
α	type I error
b	regression coefficient
cm	centimeter
km	kilometer
n	number of samples
%	percentage
µL	microliter
kg	kilogram

LIST OF ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ACAs	additional chromosomal abnormalities
AEs	adverse events
AHR	adjusted hazard ratio
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
AOE	arterial occlusive events
ATP	adenosine triphosphate
BCR-ABL1	breakpoint cluster region - Abelson murine leukaemia
BM	bone marrow
CBA	chromosome banding analysis
CCI	Charlson comorbidity index
CCyR	complete cytogenetic response
CHR	complete hematologic response
CI	confidence interval
CML	chronic myeloid leukeamia
CML-AP	accelerated phase
CML-AP/BP	accelerated phase progressed to blast phase
CML-BP	blast phase
CML-CP	chronic phase
CML-CP/AP	chronic phase progressed to accelerated phase

CML-CP/BP	chronic phase progressed to blast phase
CTIL	clinical trial import licence
CTX	clinical trial exemption
CUP	compassionate use program
DASISION	Dasatinib versus Imatinib Study In treatment-Naive CML patients
DDIs	drug-drug interactions
DMR	deep molecular response
eHIS	eHospital Information System
ELN	European LeukemiaNet
ELTS	EUTOS long-term survival score
EMA	European Medicines Agency
ENESTnd	Evaluating Nilotinib Efficacy and Safety in Clinical Trials–newly diagnosed patients
FISH	fluorescence in situ hybridization
GBD	global burden of disease
GI	gastrointestinal
GIPAP	Glivec International Patient Assistance Program
HR	hazard ratio
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
IFN-α	interferon-alfa
IQR	interquartile range
IS	international scale
JEPeM	Research and Ethics Committee of Universiti Sains Malaysia

KD	kinase domain
LDH	lactate dehydrogenase
LML	log minus log
LR	likelihood ratio
LTFU	lost to follow-up
MDACC	MD Anderson Cancer Center
MMR	major molecular response
MNCR	Malaysia National Cancer Registry Report
MOH	Ministry of Health
MPN	myeloproliferative neoplasm
MPR	medication possession ratio
MR	molecular response
MREC	National Medical Research and Ethics Committee
MyPAP	Malaysian Patient Assistance Program
MySCan	Malaysian Study on Cancer Survival
N/A	not available
NCCN	National Comprehensive Cancer Network
NHID	National Health Information Database
NIH	National Institutes of Health
NMRR	National Medical Research Registry
NRD	National Registration Department
OD	odd ratio
OS	overall survival
PBR	population-based registry

PFS	progression free survival
Ph+	Philadelphia chromosome positive
PPI	proton pump inhibitor
PS	Power and Sample Size calculations
RT-PCR	reverse transcriptase-polymerase chain reaction
SD	standard deviation
SE	standard error
SEER	Surveillance, Epidemiology, and End Results-Medicare
STAMP	specifically targeting the ABL Myristoyl Pocket
TFR	treatment-free remission
TKI	tyrosine kinase inhibitor
UK	United Kingdom
UMMC	University of Malaya Medical Centre
USA	United States of America
USFDA	United States Food and Drug Administration
USM	Universiti Sains Malaysia
VIF	variance inflation factors
vs	versus
WHO	World Health Organization
1GTKI	first-generation TKI
2GTKI	second-generation TKI
3GTKI	third-generation TKI

LIST OF APPENDICES

KADAR KEMANDIRIAN KESELURUHAN DAN FAKTOR PROGNOSTIK BAGI KEMANDIRIAN PESAKIT *CHRONIC MYELOID LEUKEAMIA* DENGAN TERAPI *TYROSINE KINASE INHIBITOR* DI HOSPITAL AMPANG, SELANGOR

ABSTRAK

Pengenalan: Pengurusan *Chronic Myeloid Leukeamia* (CML) telah direvolusikan dengan kemunculan *tyrosine kinase inhibitors* (TKIs). Walaupun lebih daripada dua dekad sejak penggunaan TKI di Malaysia, namun hasil jangka panjang masih belum dikaji dengan terperinci. Pelbagai faktor boleh memberi kesan kepada prognosis dan memahami faktor ini boleh mempengaruhi pengurusan pesakit dan meningkatkan kemandirian jangka panjang. **Objektif**: Kajian ini bertujuan untuk menentukan dan membandingkan kadar kemandirian keseluruhan 10 tahun serta mengenal pasti faktor prognosis yang signifikan di kalangan orang dewasa yang didiagnosis CML dengan terapi TKI di Hospital Ampang, Selangor. **Metodologi**: Kajian kohort retrospektif ini mengkaji 389 rekod perubatan pesakit CML berusia 18 tahun dan ke atas dengan terapi TKI - termasuk imatinib mesylate atau nilotinib – antara tahun 2012 dan 2021, manakala pesakit yang menjalani transplantasi sel induk hematopoietik (TSIH) atau pesakit yang dipindahkan keluar dari Hospital Ampang dikecualikan daripada kajian. Hasil utama kajian adalah kematian dari sebarang sebab. Pemerhatian tertapis termasuk pesakit yang masih hidup diakhir kajian atau mereka yang hilang dari rawatan susulan. Masa hidup dirujuk sebagai tempoh masa (bulan) dari permulaan terapi TKI bagi pesakit CML hingga kematian.

Pemerhatian Kaplan Meier dan ujian pangkat-log digunakan dalam analisis univariat, manakala regresi bahaya berkadar Cox pelbagai faktor digunakan untuk mengenal pasti faktor prognostik yang penting untuk kemandirian. **Keputusan**: Terdapat 51 (13.1%) kematian dari sebarang sebab diakhir kajian. Pesakit disusuli selama median 74 bulan (julat antara kuartil: 58 bulan) dengan kadar anggaran kemandirian keseluruhan pada sepuluh tahun adalah 81.7%. Kadar kemandirian keseluruhan adalah signifikan lebih baik bagi umur <60 tahun (p<0.001), *Charlson Comorbidity Index* 2–3 (p<0.001), bacaan asas *blasts* <10% (p<0.001), risiko rendah bagi skor prognosis menggunakan skor kemandirian hidup jangka panjang EUTOS (ELTS) (p=0.001), fasa kronik (CML-CP) semasa diagnosis (p<0.001), tiada perubahan fasa penyakit CML (p<0.001), permulaan terapi TKI pada tahun 2012–2015 (p<0.001), permulaan dos standard bagi rejimen TKI (p=0.041), pematuhan tinggi (MPR) kepada terapi TKI (p<0.001), tidak mengalami kesan buruk yang memerlukan perubahan dos TKI (p=0.002), tiada sejarah ketidakhadiran ke rawatan susulan (p=0.015), tidak mengambil lebih dari tiga ubat serentak bersama TKI (p<0.001), tiada pertukaran terapi TKI (p=0.029), mencapai tindak balas sitogenetik lengkap (CCyR) pada 6 bulan (p=0.035), mencapai tindak balas molekular major (MMR) pada 12 bulan (p=0.035), dan 24 bulan (p<0.001). Empat faktor prognostik bagi kemandirian di kalangan pesakit CML dengan terapi TKI adalah perubahan fasa penyakit CML (nisbah bahaya terselaras (NBT)=8.43; 95% selang keyakinan (SK): 3.95, 18.01; p<0.001), masa untuk permulaan terapi TKI (100 hari) (NBT=1.22; 95% SK: 1.11, 1.35; p=0.011), pengambilan sekurang-kurangya tiga ubat serentak bersama TKI (NBT=7.59; 95% SK: 3.62, 15.91; p<0.001) dan gagal mencapai MMR pada 24 bulan (NBT=2.19; 95% SK: 1.04, 4.64; p=0.039). **Kesimpulan**: Kajian ini

menekankan pentingnya permulaan rawatan segera dan pemantauan rapi teruatamanya bagi pesakit yang mengalami perubahan fasa penyakit CML, penundaan permulaan TKI selepas diagnosis, pengambilan sekurang-kurangya tiga ubat serentak bersama TKI dan gagal mencapai MMR pada 24 bulan bagi memastikan hasil kemandirian keseluruhan yang lebih baik pada jangka panjang.

Kata kunci: kemandirian keseluruhan, *tyrosine kinase inhibitor, chronic myeloid leukaemia*

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ABSTRACT

Introduction: Chronic Myeloid Leukaemia (CML) management has been revolutionized by the advent of tyrosine kinase inhibitors (TKIs). Despite more than two decades since the introduction of TKIs in the Malaysian healthcare landscape, long term outcomes have not been rigorously studied. Various factors may impact prognosis and understanding these factors may influence patient management and improve long term outcomes. **Objective**: This study aims to estimate and compare the 10-year overall survival (OS) rates and to identify significant prognosis factors among adults diagnosed with CML on TKI therapy in Hospital Ampang, Selangor. **Methods**: This retrospective cohort study reviewed the medical records of 389 CML patients aged 18 years and above who were initiated with TKIs – including imatinib mesylate or nilotinib – between 2012 and 2021, while patients who received hematopoietic stem cell transplantation (HSCT) therapy and transferred out were excluded. The primary outcome of interest was an event of death from any cause. Censored observations were considered for patients who remained alive at the end of the study or those who were lost to follow-up (LTFU). Survival time was the duration of time (months) from the initiation of TKI therapy in CML patients to the event. Kaplan-Meier product limit estimator and log-rank test were applied for

univariable analysis, while Cox proportional hazards regression was applied in multivariable analysis to identify the significant prognostic factors for survival. **Results**: There were 51 deaths (13.1%). Patients were followed up for a median of 74 months (interquartile range (IQR): 58 months) with a 10-year overall survival rate of 81.7%. The overall survival rates were significantly better for age <60 years at the TKI therapy initiation (p<0.001), Charlson Comorbidity Index 2–3 (p<0.001), baseline blasts <10% (p<0.001), low-risk prognosis scoring with EUTOS long-term survival score (ELTS) (p=0.001), chronic phase (CML-CP) at diagnosis (p<0.001), no CML disease progression (p<0.001), year of TKI therapy initiation between 2012–2015 (p<0.001), standard dose initial TKI regimen (p=0.041), high medication possession ratio (MPR) for TKI (p<0.001), no adverse events requiring TKI dose adjustment (p=0.002), no history of follow-up defaults (p=0.015), not more than three concurrent medications with TKI therapy (p<0.001), no TKI switching (p=0.029), complete cytogenetic response (CCyR) at 6 months (p=0.035), major molecular response (MMR) at 12 months (p=0.035), and 24 months (p<0.001). Four significant independent prognostic factors of survival among CML adults with TKI therapy identified were CML disease progression (adjusted hazard ratio (AHR)=8.43; 95% confidence interval (CI): 3.95, 18.01; p<0.001), time to TKI initiation (100 days) (AHR=1.22; 95% CI: 1.11, 1.35; p=0.011), three or more concurrent medications with TKI therapy (AHR=7.59; 95% CI: 3.62, 15.91; p<0.001) and failure to achieve MMR at 24 months (AHR=2.19; 95% CI: 1.04, 4.64; p=0.039). **Conclusion**: The study emphasizes the importance of therapy initiation and close monitoring for patients experiencing CML disease progression, delayed TKI commencement post-diagnosis,

three or more concurrent medications alongside TKI, and failure to achieve MMR at 24 months to ensure improved long-term outcomes and overall survival.

Keywords: overall survival, tyrosine kinase inhibitor, chronic myeloid leukaemia

CHAPTER 1

INTRODUCTION

1.1 Overview of Chronic Myeloid Leukaemia

Chronic myeloid leukaemia (CML) is a type of myeloproliferative neoplasm (MPN) disorder involving the malignant expansion of blood-forming cells in the bone marrow. Globally, CML accounts for 15% of leukaemia among adults, with an incidence between 1-2 cases per 100,000 population (Olanrewaju Osho *et al.*, 2021). Meanwhile, in Malaysia, as reported by Malaysia National Cancer Registry Report (MNCR) 2012–2016, leukaemia including lymphoid, myeloid and other unspecified types is the sixth most common cancer, with Malays having the highest incidence rate followed by Chinese and Indians in both sexes.

Limited reliable statistics are available on the precise prevalence of CML. However, in the last two decades, the dynamic increase in prevalence among CML patients has been observed due to the improved life expectancy and overall survival, especially after the breakthrough of imatinib mesylate and other Tyrosine Kinase Inhibitors (TKIs) (Shallis *et al.,* 2020; Dreyling, 2021; Hu *et al.,* 2021). In the United States of America (USA), the number of CML cases, which was projected to be 30,000 cases in 2000, has climbed by roughly 8,600 cases/year and is expected to reach more than 150,000 cases in 2022 (Jabbour & Kantarjian, 2022). Meanwhile, as reported in the epidemiology survey in France, CML prevalence is forecast to reach 24 and 30 cases per 100,000 population in 2030 and 2050, respectively, as opposed to estimates of 6 per 100,000 population in 2002 (Delord *et al.,* 2018).

Comorbidities, particularly those associated with severe organ failure and cognitive impairment, along with older age, are crucial factors in therapy selection. These factors not only affect overall survival but may also lead to lower treatment tolerability (Hochhaus *et al.,* 2020; Dreyling, 2021). Earlier therapy options for CML in the pre-TKI era have been non-specific oral medications such as busulfan and hydroxyurea, which had moderate efficacy and interferon-alfa (IFN-α) given subcutaneously or intramuscularly, which resulted in suppression of the Philadelphia-positive (Ph+) clones. Nevertheless, IFN-α therapy is linked to serious neurotoxicity, including immune-mediated complications, depression, and cognitive impairment, as well as elevated liver enzymes and poor treatment compliance (Dreyling, 2021). Another therapy alternative for CML is hematopoietic stem cell transplantation (HSCT). However this treatment is primarily offered to fit young patients with donor availability.

The latest reports from the American Cancer Society showed a substantial enhancement in the survival rate of CML patients in the USA. The current 5-year relative survival rate, which compares the overall survival of the studied population to that of the corresponding general population, is three times higher than it was in the mid-1970s (22%), with a substantial reduction of annual mortality from 10%-20% to 1%-2% (Sasaki *et al.,* 2015; Jabbour & Kantarjian, 2022; American Cancer Society. Cancer Facts & Figures, 2024).

CML could impact any age group; nevertheless, the incidence increases steadily with age, as more than 20% of patients are above 70, whereas only 5% are children and adolescents. The median age upon diagnosis of around 56 up to 62

years has been reported among CML patients in Western countries (Hochhaus *et al.,* 2020; Dreyling, 2021); meanwhile, a lower median age of less than 50 years in Africa and Asia (Hochhaus *et al.,* 2020). Besides age, differences in CML incidence can be seen between genders, with males more likely than females to develop CML. A male-to-female ratio that ranges from 1.2 to 1.7 is described by (Dreyling, 2021), but the gender gap is less pronounced in lower age groups.

The long-term or possibly indefinite TKI therapy among most CML patients, even minimal, may cause adverse effects such as fatigue, nausea, muscle and joint pain, and gastrointestinal issues, which could negatively impact therapy adherence. A previous study reported that health-related quality of life (HRQoL), such as mood, general health, enjoyment of life and overall relationships, had negatively impacted CML patients who experienced adverse effects (Nardi *et al.,* 2022). The constant need for regular monitoring, follow-up visits, and potential treatment adjustments may also add to emotional distress and financial burden and family members as patients may experience anxiety, depression, or fear of disease progression. A study has shown that irregular follow-up visits for molecular monitoring are strongly associated with poor clinical outcomes among CML patients from resource-poor countries (Dreyling, 2021). Besides the costly therapy, ongoing support of time, expertise and coordination with other healthcare professionals may pose an economic burden to healthcare providers; thus, a selective first-line TKI treatment is essential (Wan Puteh *et al.,* 2022).

1.2 Problem statement

The advent of TKI therapy, which exhibits a remarkable improvement in cytogenetic and molecular responses compared to IFN-α and conventional chemotherapy (Lim, Eng & Chan, 2017), has transformed the treatment paradigm for patients with CML (Morita & Sasaki, 2021). Furthermore, when TKI therapy is properly initiated, patients diagnosed with CML can anticipate a nearly normal life expectancy (Cortes, Rea & Lipton, 2019).

Nevertheless, despite the high success rates, a fraction of CML patients are still experiencing suboptimal outcomes to TKI therapy that lead to the progression of CML to the accelerated or fatal blast phases and decreased overall survival (Breccia *et al.*, 2021). Extensive studies to determine the survival and prognostic factors for TKIs among CML patients in real-world settings have been conducted around the globe (Ono *et al.*, 2020; Breccia *et al.*, 2021; Specchia *et al.*, 2021), but limited information can be obtained for Malaysia as the published studies for TKIs therapy were mainly focusing on the BCR-ABL of the kinase domain (KD) mutations (Elias *et al.*, 2014; Yusoff *et al.*, 2018), additional chromosomal abnormalities (ACAs) (Siti Mariam *et al.*, 2022), treatment and response-related factors (Bee *et al.*, 2017) and suboptimal adherence (Tan *et al.*, 2020).

Based on a local qualitative study, CML patients who took either imatinib or nilotinib occasionally complained about their disrupted daily activities due to the number of adverse events (AEs) experienced and have minimal knowledge of how TKIs control their illness and the parameters monitored for their treatment outcome (Lim, Eng & Chan, 2017).

A retrospective cohort study was performed in a local setting to evaluate the survival of 70 CML patients treated with imatinib from the University of Malaya Medical Centre (UMMC), Malaysia. The study, which examined molecular and cytogenetic responses and patient characteristics, concluded that the 10-year overall survival rate was 94.3%. At the six-month mark, patients with a BCR-ABL1 level ≤10% exhibited a markedly superior overall survival in comparison to those with a BCR-ABL1 level > 10% (p=0.041) (Bee *et al.*, 2017). However, the study conducted by (Bee *et al.*, 2017), which recruited CML patients in 2006, had limitations, including the inclusion of only imatinib as front-line therapy, a focus on a few prognostic factors, and a small sample size (n=70) due to the limited accessibility for CML care at UMMC. This led to disparities in the study findings compared to the existing literature. Additionally, poor estimation of survival probabilities in the study, which failed to account for the confounding effects of other covariates with Kaplan-Meier's method, may have resulted in either overestimation or underestimation of the results (Stel *et al.*, 2011). Thus, a comprehensive determination of the survival and prognostic factors based on the patient-related, clinical-related and treatment and response-related factors along with adjustment of the potential confounders among CML patients with TKI therapy, is needed.

1.3 Rationale of the study

The overall survival rates and determination of the prognostic factors of CML after initiation of TKI therapy could provide valuable information to the healthcare professionals in treatment decisions for long-term management of CML by

identifying suboptimal responders, improving their prognosis, and provide insights for the development of personalised therapeutic strategies to overcome treatment challenges in the future.

The yearly increase in the price of TKIs, which is also known as one of the most expensive outpatient cancer drugs available in Malaysia, poses a financial challenge to the Malaysian government. A majority of CML patients rely heavily on subsidised treatment; an understanding of TKI therapy's effectiveness in prolonging survival may help policymakers and stakeholders with resource allocation, planning for the needs of CML patients and optimising the healthcare delivery for this population.

Prognostic information may improve CML patients' understanding of the possible outcomes and long-term prognosis linked to their illness and therapy. This knowledge enables patients to make well-informed treatment choices, anticipate their future needs, and share decision-making with their healthcare providers.

CML therapy with TKIs has been available since 2003 through the Glivec International Patient Assistance Program (GIPAP), followed by the initiation of the Malaysian Patient Assistance Program (MyPAP) scheme in 2007 in Malaysia. However, comprehensive studies have yet to be published to determine the overall survival and prognostic factors (including patient-related, clinical-related, and treatment and response-related factors) among CML patients at Hospital Ampang, Selangor. This hospital is known as the National Reference Centre for Haematology, serving approximately half of the CML patients nationally. Therefore, this study aims to significantly address the knowledge gap regarding the prognostic factors

associated with TKI therapy in Malaysian CML patients. Currently, there is limited understanding of the specific factors that influence the long-term outcomes of CML patients on TKI therapy within the Malaysian population. This study will provide critical insights into patient outcomes, treatment effectiveness, and how these factors vary in the local context, thus enhancing the ability to make informed clinical decisions and optimize patient care.

1.4 Research questions

1. What is the 10-year overall survival rate of CML adults treated with TKI in Hospital Ampang?
2. Are there any significant differences in the 10-year survival rates of CML adults treated with TKI in Hospital Ampang according to the categorical factors of patient-related, clinical-related and treatment and response-related?
3. What are the prognostic factors for survival among CML adults treated with TKI in Hospital Ampang?

1.5 Study objectives

1.5.1 General objective

To study the survival rate and prognostic factors for survival among CML adults after initiation of TKI therapy in Hospital Ampang.

1.5.2 Specific objectives

1. To estimate the 10-year overall survival rate of CML adults treated with TKI in Hospital Ampang.

2. To compare the 10-year survival rates of CML adults treated with TKI in Hospital Ampang according to the categorical factors of patient-related, clinical-related and treatment and response-related.

3. To identify the prognostic factors for survival among CML adults treated with TKI in Hospital Ampang.

1.6 Research hypothesis

1. There are significant differences in the 10-year survival rates among CML adults treated with TKI in Hospital Ampang according to the categorical factors of patient-related, clinical-related and treatment and response-related.

2. The prognostic factors among CML adults treated with TKI in Hospital Ampang are patient-related factors, clinical-related factors and treatment and response-related factors.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Prior to conducting the literature search, search terms or phrases were determined. Boolean operators and keywords were employed in the literature search strategies to enhance the search precision. Phrases used in phrase searching were "survival of chronic myeloid leukaemia patients after tyrosine kinase inhibitor therapy" and "prognostic factors of chronic myeloid leukaemia patients after tyrosine kinase inhibitor therapy". Among the keywords used were “Adult” AND “CML” AND “TKI” AND “survival rates” AND “Malaysia”, “Adult” AND “CML” AND “tyrosine kinase inhibitor” AND “prognostic factors” AND “Cox” and “Adult” AND “CML” AND “TKI” AND “prognostic factors” AND “Cox".

For citation search, the author's name and the article's title were utilized to locate relevant citations. The search engines used were PubMed, Springer Link, ScienceDirect, Blood and Google Scholar. Related articles found were imported to the Mendeley reference manager library.

2.2 CML

2.2.1 Definition of CML

CML, also known as chronic myelogenous leukaemia or chronic granulocytic leukaemia, is a form of leukaemia under the family of MPNs that occurs from the reciprocal translocation between the long arms of Abelson murine leukaemia (ABL1) gene from chromosome 9 with breakpoint cluster region (BCR) gene from

chromosome 22. These translocations resulted in the Ph chromosome, specifically the fusion BCR-ABL1 gene at chromosome 22. CML is predominantly characterised by the excessive and uncontrolled proliferation of primarily myeloid cells in the bone marrow and the accumulation of these cells in the PB due to the aberrant tyrosine kinase protein activity (Shallis *et al.*, 2020; Olanrewaju Osho *et al.*, 2021; PDQ Adult Treatment Editorial Board, 2023).

2.2.2 Risk factors of CML

The cause of CML is poorly understood. One of the prominent risk factors associated with CML is exposure to ionising radiation in individuals who survived the Hiroshima atomic bomb (Dreyling, 2021). Apart from radiation, the Global Burden of Disease (GBD) Study 2019 identified smoking (12.2%), high body mass index (5%), occupational exposure to benzene (0.9%), and occupational exposure to formaldehyde (0.3%) as four risk factors associated with CML (Hu *et al.*, 2021).

Case-control research in the American population suggested a weak association of smoking in both genders of CML patients. The analysis showed that the risk of CML increased steadily as pack-years of smoking increased and only began to decline after 30 years of smoking cessation (Musselman *et al.*, 2013). Meanwhile, a separate study of de novo CML cases and controls demonstrated a statistically significant association between obesity and the risk of developing CML. According to the multivariable analysis, obesity was linked to a 4-fold increase in the risk of CML at age 25 (Odd Ratio (OR)=4.29; 95% CI, 1.63, 11.3); meanwhile, a 5-fold increase in the risk of CML was seen when someone was moderate/severely obese at age 40 (OR=5.12; 95% CI, 1.92, 13.6) (Strom *et al.*, 2009).

2.2.3 Clinical manifestations

The clinical features upon diagnosis of CML vary between individuals and depend on the diagnosis stage of the disease. Since CML is frequently detected by post-routine blood tests, it has been reported that up to 50% of CML patients are asymptomatic. There are approximately 90-95% of newly diagnosed CML patients present at CP with typical signs and symptoms of malaise, easy satiety, weariness, weight loss, and discomfort or fullness in the upper left area of the quadrant, primarily due to anaemia and splenomegaly. Meanwhile, rare clinical symptoms include thrombosis, retinal haemorrhages, upper gastrointestinal ulceration and bleeding, and involvement of extramedullary disease with immature blast cells in blast crisis (Cortes, Pavlovsky & Saußele, 2021; Jabbour & Kantarjian, 2022).

2.2.4 Diagnosis of CML

CML is frequently detected during routine physical examinations and blood tests. The diagnosis of CML is relatively simple and can be confirmed by a peripheral blood (PB) film through qualitative reverse transcriptase-polymerase chain reaction (RT-PCR), which is essential for identifying the type of BCR-ABL1 transcripts and cytogenetic analysis by chromosome banding analysis (CBA) from bone marrow (BM) aspirate to detect the presence of the Philadelphia chromosome-positive (Ph+), specifically the t(9;22)(q34.1;q11.2) translocation (Arber *et al.*, 2016; Jabbour & Kantarjian, 2022).

Approximately 2-4% of CML patients have atypical BCR-ABL1 transcripts, such as ABL1 exon2 (e13a3 or e14a3) or atypical BCR breakpoints (e.g., e1a2, e6a2, e8a2, or e19a2), where routine primer sets used in qualitative RT-PCR may fail to detect

rare BCR-ABL transcripts. Therefore, cytogenetic analysis should be performed to assess the response of the rare BCR-ABL transcripts. Meanwhile, for the validation of the phase of disease among suspected CML patients, morphologic analysis and flow cytometry from BM aspirate must be performed to assess the proportion of blast cells and basophils (Hochhaus *et al.*, 2020).

Detection of clonal cytogenetic evolution in the Ph chromosome, also known as ACAs with bone marrow cytogenetics or PB analysis with fluorescence in situ hybridization (FISH) during the initial workup stage is also advisable as the presence of ACA/Ph+ may impact the prognosis and overall survival of CML patients (Kristina Gregory *et al.*, 2023).

2.2.5 Classification of CML

Prior to the development of selective TKI therapy, the natural course of untreated CML was biphasic or triphasic, consisting of an initial, indolent chronic phase (CML-CP) followed by a blast phase (CML-BP), with or without a subsequent accelerated phase (CML-AP). The key clinicopathological features of CML are widely classified based on certain criteria described by the World Health Organization (WHO), European LeukemiaNet (ELN) and National Comprehensive Cancer Network (NCCN). Table 2.1 shows the different diagnostic criteria as measured on PB smears or bone marrow (BM) samples for the various stages of CML (Baccarani *et al.*, 2013; Arber *et al.*, 2016; Cortes, Pavlovsky & Saußele, 2021; Kristina *et al.*, 2024).

Table 2.1 Criteria for various stages of CML as measured on blasts (%) of PB smears or BM samples

	WHO	ELN & NCCN [MD Anderson Cancer Center (MDACC)]
CP	Blasts <10% (PB or BM)	Blasts <15% (PB or BM)
AP	Blasts 10-19% (PB or BM)	Blasts 15-29% (PB or BM)
	Basophils ≥20% (PB)	Basophils ≥20% (PB)
BP	Blasts ≥20% (PB or BM)	Blasts ≥30% (PB or BM)

2.2.6 Treatment and management of CML

Before the 20th century, drug therapy for CML was only available with non-targeted medications such as busulfan, hydroxyurea, and interferon-alfa (IFN-α). In nearly 25–30% of CML patients receiving low-dose chemotherapy, cytarabine combined with IFN-α achieved a complete cytogenetic response (CCyR), with a 10-year overall survival probability of 78%. Despite the reduction of Ph+ cells and increased survival, the substantial adverse effects of IFN-α hindered long-term usage. However, in the early 2000s, the advent of TKIs effectively blocked the BCR-ABL1 oncoprotein, inhibiting the proliferation of the malignant clone and significantly changing the treatment landscape for CML. This 'targeted' therapy altered the natural disease progression of CML, resulting in an increase in the 10-year survival rate to 80–90% (Cortes, Pavlovsky & Saußele, 2021; Jabbour & Kantarjian, 2022). Currently, the four front-line TKI therapy options approved by the United States Food

and Drug Administration (USFDA) and European Medicines Agency (EMA) for initial management of CML-CP are imatinib, dasatinib, nilotinib, and bosutinib.

2.2.7 TKIs

2.2.7(a) TKIs therapy for CML in Malaysia

In Malaysia, there are only three TKI therapies approved for CML under the National Drug Formulary: imatinib as front-line in the year 2008, nilotinib as second-line in the year 2012, subsequently also as first-line therapy and ponatinib as third-line in the year 2021 (Pharmaceutical Services Programme, Ministry of Health Malaysia, 2024). Regarding the registration status of TKIs, Glivec (imatinib) in 100 mg and 400 mg formulations was first registered in 2006, followed by Tasigna (nilotinib) in 2008, with strengths of 200 mg and 150 mg registered in 2011. Subsequently, Iclusig (ponatinib) was registered in 2019 with strengths of 15 mg and 45 mg, and Scemblix (asciminib) followed in 2023 with strengths of 20 mg and 40 mg. As for Sprycel (dasatinib), it was initially registered in 2007, but its registration expired in 2024. Currently, only generic forms with strengths of 50 mg and 70 mg were registered in early 2024 (National Pharmaceutical Regulatory Agency, 2024b).

2.2.7(a)(i) Imatinib mesylate

Imatinib mesylate, the first-generation TKI (1GTKI), is the gold standard for front-line therapy. Approved by the EMA in 2001 for CML patients with unsatisfactory responses to IFN-α (Cortes, Pavlovsky & Saußele, 2021), it became available in Malaysia starting in 2003 (Tan *et al*., 2017). Generally, the standard dosage of imatinib in Malaysia is 400 mg for CML-CP and 600 mg for CML-AP or CML-BP, taken

once daily orally with dose increments up to 800 mg taken as 400 mg twice daily (Novartis Corporation (Malaysia), 2022).

2.2.7(a)(ii) Nilotinib

Nilotinib is the second-generation TKI (2GTKI) which showed improved inhibitory potency in comparison to imatinib due to the 30-50 times higher affinity to the adenosine triphosphate (ATP) binding site of BCR-ABL1 (Jabbour & Kantarjian, 2022). In the Evaluating Nilotinib Efficacy and Safety in Clinical Trials–newly diagnosed patients (ENESTnd) study, at 24 months of assessment, nilotinib groups (nilotinib 300 mg and 400 mg twice daily) had shown significantly higher major molecular response (MMR) (71% and 67%) compared to imatinib 400 mg daily (44%) ($p<0.001$). The approved recommended dose for nilotinib in Malaysia is 300 mg twice daily orally for first-line CML-CP and 400 mg twice daily for second-line CML-CP who had resistance or intolerance to prior therapy (Novartis Corporation (Malaysia), 2021).

2.2.7(a)(iii) Dasatinib

Dasatinib is a 2GTKI that exhibits greater potency than imatinib and is effective against various imatinib-resistant BCR-ABL1 mutants, such as Y253H, E255V/K, and F359V/I/C. According to Dasatinib versus Imatinib Study In treatment-Naive CML patients (DASISION) trial, which compared dasatinib at a dose of 100 mg once daily to imatinib at a dose of 400 mg once daily over a minimum follow-up period of 5 years, demonstrated notable advantages with dasatinib. The early molecular response (EMR) rate (84%), the rate of achieving MMR by one year (46%), and the 5-year cumulative probabilities of attaining MMR (76%) and MR4.5 (42%) were all significantly higher. The approved recommended dosage for dasatinib is 100

mg once daily orally for CML-CP and 70 mg twice daily for advanced-phase CML. However, due to the risk of pleuro-pulmonary toxicity, dasatinib is contraindicated as a first-line management option for CML patients with respiratory failure and a history of concurrent pleuropulmonary or pericardial diseases (Cortes *et al.,* 2016; Hochhaus *et al.,* 2020).

2.2.7(a)(iv) Ponatinib

Ponatinib is a potent third-generation TKI (3GTKI) approved by the USFDA in 2012 for the treatment of adult patients with CML-CP, CML-AP, or CML-BP that is resistant or intolerant to prior TKI therapy. However, due to substantial safety concerns, including the possibility of arterial occlusive events (AOE), it was briefly voluntarily withdrawn from the market. Later, in 2013, ponatinib was re-approved for limited indications, specifically for CML patients with the 'gatekeeper' T315I mutation. In 2018, its indication was expanded to include CML-CP patients with resistance or intolerance to at least two prior TKIs, as noted by Dianne Pulte *et al.* (2022), and for patients with CML-AP or CML-BP for whom no other TKI is indicated (Kristina *et al.,* 2024). Additionally, in patients with resistance to a 2GTKI without specific mutations, ponatinib is preferred over alternative 2GTKIs unless cardiovascular risk factors preclude its use (Hochhaus *et al.,* 2020). In Malaysia, the approved recommended dose for ponatinib is 45 mg once daily orally (Otsuka Pharmaceutical Co. Japan, 2021).

2.2.7(a)(v) Asciminib

Asciminib, a first-in-class BCR-ABL1 inhibitor specifically targeting the ABL Myristoyl Pocket (STAMP), is a newer 3GTKI therapy option for CML-CP patients. In a

phase III RCT, asciminib exhibited greater efficacy and a more favourable safety profile in comparison to bosutinib. The MMR rate at week 24 was 25.5% with asciminib and 13.2% with bosutinib. After adjusting for major cytogenetic response (MCyR) at baseline, the difference in MMR rate between treatment arms was 12.2% (95% CI: 2.19, 22.30; p=0.029), with fewer grade ≥3 adverse events (50.6% vs 60.5%) and adverse events that resulted in treatment discontinuation (5.8% vs 21.1%) observed with asciminib than with bosutinib (Rea *et al.,* 2021).

The approved recommended dose in Malaysia is 40 mg taken orally twice daily for CML-CP patients who were previously treated with two or more TKIs and 200 mg taken orally twice daily for CML-CP patients with the T315I mutation (Novartis Corporation (Malaysia), 2023).

2.2.7(b) TKIs availability and accessibility in Malaysia

Since 2003, Malaysia has had access to the GIPAP scheme, which was then replaced by The MyPAP in 2007. MyPAP is a public-private collaboration between the Ministry of Health (MOH) Malaysia and the pharmaceutical company Novartis. It is operated by The Max Foundation (Edmonds, Washington), a non-profit global health organization with assistance from the Malaysian Society of Haematology. Most CML patients in Malaysia are treated with TKI at no charge with funding from government aid through MyPAP. The two TKI therapies available under MyPAP are imatinib and nilotinib (Lim, Eng & Chan, 2017; Wan Puteh *et al.,* 2022).

Although dasatinib is not listed in the National Drug Formulary in Malaysia, since 2011, a few CML patients who failed imatinib therapy have accessed dasatinib at no cost through a compassionate use program (CUP) (Win Kuan & Sudau Michael,

2018). The CUP is a program that provides access to the investigational product (active ingredient or placebo, being investigated as a reference in a clinical trial) after the clinical trial has ended but before the product is registered in Malaysia. Only participants in the approved clinical trial involving a Clinical Trial Import Licence (CTIL) and Clinical Trial Exemption (CTX) are eligible for this program on a named-patient basis (National Pharmaceutical Regulatory Agency, 2024a).

Lastly, ponatinib and asciminib were also made available to CML patients through a CUP that began in 2016 (Win Kuan & Sudau Michael, 2018) and 2021, respectively.

2.2.8 Management of therapy response

Regular monitoring once TKI therapy is initiated is necessary to evaluate therapy response and determine the most necessary interventions based on the timely success of hematologic, cytogenetic, and molecular milestones. The response for TKI is primarily measured based on hematologic response criteria. Once a complete hematologic response (CHR) is established, periodic evaluation of BCR-ABL1 by cytogenetic and molecular studies is recommended (Radich & Mauro, 2017; Morita & Sasaki, 2021). APPENDIX A and APPENDIX B highlighted the criteria for different therapy responses of CML guidelines on TKI therapy, and monitoring response to TKI therapy and mutational analysis, respectively (Kristina *et al.,* 2024). Meanwhile, Table 2.2 illustrates the targeted milestones expressed as BCR-ABL1^{IS} by ELN 2020.

Table 2.2 Milestones for treating CML expressed as BCR-ABL1^{IS} by ELN 2020

	Optimal	Warning	Failure
Baseline	N/A	High-risk ACA, high-risk ELTS score	N/A
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR) [a]	>1%, resistance mutations, high-risk ACA

[a] Loss of MMR (BCR-ABL1^{IS}>0.1%) indicates failure after TKI discontinuation known as treatment-free remission (TFR)
A change of treatment may be considered if MMR is not reached by 36–48 months

2.2.9 Baseline prognostic scores

According to ELN 2020 Treatment Recommendations for CML, Sokal, Euro (Hasford), EUTOS, or EUTOS long-term survival score (ELTS) are four prognostic scoring systems that refer to patient baseline characteristics to facilitate the selection of TKIs (Hochhaus *et al.,* 2020).

The Sokal prognostic score was developed in 1984 based on spleen size, platelet count, the proportion of blasts in PB, and the age of chemotherapy patients. However, after the approval of IFN-α for CML therapy, SOKAL scoring could not discriminate the overall survival for intermediate and high-risk groups, prompting the new prognostic score called Euro, also known as Hasford. Euro (Hasford) used all four parameters from SOKAL, adding PB eosinophil and basophil percentage. After the discovery of TKI therapy, the EUTOS score that calculated the risk based on the spleen

size and PB basophil percentage was introduced due to the ability to stratify the risk between imatinib and IFN-a groups significantly. Finally, the ELTS was developed according to the same parameters as the Sokal score to predict the risk of CML-related death (Morita & Sasaki, 2021).

2.3 Survival rates of CML adults after initiation of TKI therapy

The current study primarily aims to assess 10-year overall survival rates among CML patients. However, it is essential to consider these findings by comparing them with overall survival rates reported in previous studies that span various durations. While our focus remains on the decade-long survival outcomes, previous research has provided valuable insights into survival rates over different timeframes. These studies offer a comprehensive understanding of survival trends, which help to benchmark and interpret the 10-year survival data presented in this study. However, due to the extensive list of studied variables, it should be noted that not all survival rates will be reported in this section.

2.3.1 Overall survival

Significant improvements in survival expectancy among adults with CML have been documented following the initiation of TKI therapy over the last decade. In the earlier years of imatinib mesylate therapy, Kantarjian *et al.* (2006) conducted a comparative retrospective analysis involving 650 CML patients treated with interferon-based regimens from 1982 to 1997 and 279 CML patients treated with imatinib mesylate from 2000 to 2004. The findings revealed a significant

improvement in survival rates, with estimated 3-year survival rates of 96% on imatinib mesylate compared to 81% on interferon ($p<0.01$).

Kalmanti *et al.* (2015) provided comparable evidence from the German CML Study IV clinical trial, which included 1503 recently diagnosed CML-CP patients from five treatment groups. These patients received either imatinib 400 mg, imatinib 400 mg + IFN, imatinib 400 mg + cytarabine, imatinib post IFN failure, or imatinib 800 mg, resulting in a 10-year overall survival of 84% (95% CI: 82, 86).

A retrospective study based on the two population-based cancer registries in Italy demonstrated an improvement in the 5-year of disease-specific survival for CML from 47.3% (95% CI: 38.5, 55.5) to 80.8% (95% CI: 74.5, 85.8) after the introduction of TKIs (Di Felice *et al.,* 2018).

A Nigerian prospective cohort study on 527 CML patients receiving imatinib under the enrollment of the GIPAP was followed for 10 years to assess cumulative survival and determinants associated with overall survival. The 1-year, 3-year and 5-year survival rates observed for patients in all stages of CML were 95%, 90% and 75% respectively, with a median survival of 106 months (95% CI: 92, 120) (Oyekunle *et al.,* 2016)). Meanwhile, a much larger survival GIPAP assessment involving 53,878 CML patients around the globe reported superior 5-year and 7-year survival rates of 90.0% (95% CI: 89.7, 90.3) and 87.8% (95% CI: 87.39, 88.19) respectively (Umeh *et al.,* 2020).

Recent retrospective cohort literature from the National Health Information Database (NHID) of South Korea involving 2,870 adults with CML treated with either imatinib, dasatinib, nilotinib, or radotinib between 2005 and 2013 had demonstrated

5- and 10-year overall survival rates of 87.1% (95% CI: 84.3, 89.4) and 77.3% (95% CI: 75.0, 79.4) respectively (Kim *et al.,* 2021).

Meanwhile, in Malaysia, similar excellent results were seen in a single real-world medical centre involving 70 CML patients either in CP or AP treated with imatinib. The 10-year overall survival reported was 94.3% (Bee *et al.,* 2017). The summary of the overall survival rates is presented in Table 2.3.

Table 2.3 Summary of studies reporting overall survival rates in CML adults with TKI therapy

Country (Authors/Year)	**Study Design (n)**	**Key findings**
United States (Kalmanti *et al.*, 2015)	Comparative retrospective cohort: IFN-α :1982–1997 (n=650) Imatinib: 2000–2004 (n=279)	3-year survival rates: IFN-α: 81.0% Imatinib: 96.0% (p<0.01)
Germany (Kalmanti *et al.*, 2015)	Randomized trial 2002–2012 (n=1,503)	10-year survival rates: 84% (95% CI: 82, 86)
Italy (Di Felice *et al.*, 2018)	Retrospective cohort 1996–2012 (n=357)	5-year of disease-specific survival: 80.8% (95% CI: 74.5, 85.8)
Nigeria (Oyekunle *et al.*, 2016)	Prospective cohort 2003–2013 (n=527)	1-year survival rate: 95% 3-year survival rate: 90% 5-year survival rate: 75%
Global GIPAP (Umeh *et al.*, 2020)	Retrospective cohort 2001–2014 (n=53,878)	5-year survival rates: 90.0% (95% CI: 89.7, 90.3) 7-year survival rates: 87.8% (95% CI: 87.39, 88.19)
South Korea (Kim *et al.*, 2021)	Retrospective cohort 2005–2016 (n=2,870)	5-year survival rates: 87.1% (95% CI: 84.3, 89.4) 10-year survival rates: 77.3% (95% CI: 75.0, 79.4)
Malaysia (Bee *et al.*, 2017)	Retrospective cohort 2007–2016 (n=70)	10-year survival rates: 94.3%

2.3.2 Patient-related factors

2.3.2(a) Age

Socio-demographic characteristics significantly influence the survival rates of CML patients receiving TKI therapy. An American cohort study by Kantarjian *et al.* (2012) demonstrated that survival probabilities decrease with age. Specifically, patients aged <60 had a 10-year overall survival rate of 75.0%, compared to 55.0% for those aged ≥60 (log-rank p<0.001). Similarly, a study by Sasaki *et al.* (2015) in the USA reported 10-year overall survival rates of 90.0% (95% CI: 84.4, 95.6) for patients aged 15–44 and 59.0% (95% CI: 44.5, 73.4) for those aged 65–84 (log-rank p<0.001). Additionally, a retrospective study in South Korea by Kim *et al.* (2021) found that CML patients aged >50 years had worse survival outcomes than those aged ≤50 years when treated with TKI (log-rank p<0.001). These consistent findings across different studies highlight the significant impact of age on the survival of CML patients.

2.3.2(b) Comorbidities

Numerous studies conducted in real-life settings have identified that comorbidities at diagnosis represent a significant cause of mortality in patients with CML. A high Charlson Comorbidity Index (CCI) has been associated with lower overall survival rates. In a retrospective study conducted in Brazil, the probabilities of overall survival at 10 years for patients with CCI 2, 3, 4, and ≥5 were observed to be 81.0% (95% CI: 73.0, 89.0), 77% (95% CI: 63.0, 100.0), and 69% (95% CI: 53.0, 85.0), and 62.0% (95% CI: 38.0, 86.0), respectively (Engelbrecht *et al.,* 2019).

Similarly, findings from the German CML Study IV clinical trial conducted by Saußele *et al.* (2015) revealed distinct eight-year survival probabilities for patients

with differing CCI. Specifically, patients with CCI 2 exhibited an 8-year survival probability of 93.6% (95% CI: 91.0, 95.8), contrasting starkly with the markedly lower survival probability of 46.4% (95% CI: 31.5, 61.7) observed in patients with CCI ≥7.

Moreover, a prospective cohort study conducted in Japan, as reported by Ono *et al.* (2020), further substantiated this trend. Patients with varying CCI demonstrated disparate five-year overall survival rates within the entire cohort. Patients with CCI 2 exhibited a notably higher overall survival rate of 94.4% compared to those with CCI 3 and ≥4, who displayed overall survival rates of 89.0% and 72.8%, respectively (log-rank p<0.001).

2.3.3 Clinical-related factors

2.3.3(a) Basophils

Elevated basophil count, particularly a high percentage of basophils, has been associated with shorter overall survival and later stages in CML (CML-AP and CML-BP) (Kristina *et al.,* 2024). However, a population-based registry (PBR) study involving CML-AP patients across various regions in Europe reported a contrasting observation. Patients with basophils <20% had a lower 2-year survival rate (75.0%; 95% CI: 0.68, 0.82) compared to those with ≥20% (85%; 95% CI: 0.75, 0.96) (Lauseker *et al*., 2019).

2.3.3(b) Blasts count

The percentage of immature blood cells or blasts in the PB or BM is one of the most significant predictors of overall survival in CML. Poor overall survival is observed in the study by Lauseker *et al.* (2019), which reported a median survival of 1.6 years with 2-year survival rates of 44% (95% CI: 0.30, 0.65) for CML-AP with PB blasts of