

Inequality in Drug Utilization among Chronic Myeloid Leukaemia Patients in Malaysia: A Cost-Utility Analysis

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Abstract

Background: The burden of chronic myeloid leukaemia (CML) is increasing due to longer patient survival, better life expectancy of the general population, and increasing drug prices. Funding is one of the main concerns in the choice of CML medication used worldwide; thus, patient assistance programmes were introduced to ensure accessibility to affordable treatment. In this study, we evaluated CML drug distribution inequality in Malaysia through patient assistance programmes, using pharmaco-economics methods to evaluate CML treatment from the care provider's perspective. **Methods:** Patients with CML were recruited from outpatient haematological clinics at the national centre of intervention and referral for haematological conditions and a public teaching hospital. The health-related quality of life or utility scores were derived using the EuroQol EQ-5D-5L questionnaire. Costing data were obtained from the Ministry of Health Malaysia Casemix MalaysianDRG. Imatinib and nilotinib drug costs were obtained from the administration of the participating hospitals and pharmaceutical company. **Results:** Of the 221 respondents in this study, 68.8% were imatinib users. The total care provider cost for CML treatment was USD23,014.40 for imatinib and USD43,442.69 for nilotinib. The governmental financial assistance programme reduced the total care provider cost to USD13,693.51 for imatinib and USD19,193.45 for nilotinib. The quality-adjusted life years (QALYs) were 17.87 and 20.91 per imatinib and nilotinib user, respectively. Nilotinib had a higher drug cost than imatinib, yet its users had better life expectancy, utility score, and QALYs. Imatinib yielded the lowest cost per QALYs at USD766.29. **Conclusion:** Overall, imatinib is more cost-effective than nilotinib for treating CML in Malaysia from the care provider's perspective. The findings demonstrate the importance of cancer drug funding assistance for ensuring that the appropriate treatments are accessible and affordable and that patients with cancer use and benefit from such patient assistance programmes. To establish effective health expenditure, drug distribution inequality should be addressed.

Keywords: cost effectiveness analysis- chronic myeloid leukaemia- tyrosine kinase inhibitors- imatinib- nilotinib

Asian Pac J Cancer Prev, 23 (12), 4253-4260

Introduction

Medicines represent one of the most frequently used health technology components for disease prevention and treatment. More than 24% of global total health expenditure is on drug purchasing (Milani and Scholten, 2011). In developing countries, a significant amount of pharmaceutical spending is paid out-of-pocket by individuals (Du et al., 2019; Kong et al., 2010; Lu et al., 2011), which imposes a substantial financial burden on patients and presents an increased challenge for care providers, particularly for cancer drugs.

To ensure universal healthcare coverage, many countries introduced patient assistance programmes to ensure the availability of affordable treatment in sufficient quantities and to improve access to medicines likely to

have a high budget influence either due to high treatment cost per patient or large volumes of use (Lu et al., 2015). Nonetheless, such programmes are typically of limited duration. Thereafter, some countries shifted the financial burden to their governments, whereas a few opted for self-paying patients to pay for the medicines, which may lead to catastrophic health expenditure (CHE). Such a financial burden would affect the patient's quality of life in addition to the other effects of the economic burden of health conditions, such as multiple hospital admissions, increased length of hospital stay, hospital investigations, and medical procedures.

Chronic myeloid leukaemia (CML) is a chronic debilitating health condition that exemplifies a substantial burden requiring lifelong treatment, recurrent hospital appointments, and costly medication. CML accounts for

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15% of all leukaemias, where its incidence varies globally from 0.4 to 1.5 per 100,000 population (Au et al., 2009; Besa et al., 2014; Kim et al., 2010). Nevertheless, the CML disease burden is increasing due to longer patient survival, better life expectancy of the general population, and increasing drug prices. A group of targeted therapy drugs, tyrosine kinase inhibitors (TKI) substantially improve the survival and life of patients with CML, ensuring that they achieve the life expectancy of the normal population (Dalziel et al., 2004; Druker et al., 2006; Reed et al., 2004; Rochau, Klubenschaedl, et al., 2015). Unfortunately, TKI are among the most expensive outpatient cancer drugs available. When it became available in 2001, the first-generation TKI imatinib cost approximately USD30,000 per year of treatment (Chhatwal et al., 2015). By 2012, the price had tripled to USD92,000. The second- and third-generation TKI cost approximately USD100,000 in 2010 or more annually (Chhatwal et al., 2015).

In Malaysia, the Glivec International Patient Assistance Program (GIPAP) has been available since 2003. It transitioned in 2007 into the Malaysian Patient Assistance Programme (MyPAP) (Kuan et al. 2018). MyPAP is a public-private partnership between the Ministry of Health Malaysia (MOH) and the pharmaceutical company Novartis and is managed by a non-profit global health organisation (The Max Foundation) with the support of the Malaysian Society of Haematology. Currently, most patients with CML in Malaysia are managed under government funding assistance via MyPAP. The MyPAP CML registry recorded the current CML prevalence as 1,646 (up until December 2018). In Malaysia, TKI medication is purchased under the Patient Access Scheme (PAS) via the MOH Pharmaceutical Services Programme. To date, only imatinib and nilotinib, first- and second-generation TKI, respectively, are approved for treating CML under the MOH medicine formulary. Nonetheless, the TKI quantity provided under this scheme is limited and there is a long waiting list for patients with CML before they can access the medication.

Accordingly, the study objective was to evaluate CML drug distribution inequality through patient assistance programmes in Malaysia by using pharmaco-economics methods to evaluate the treatment cost for patients with CML from the care provider's perspective. This study highlights the significance of effective and efficient health expenditure of CML treatment and aims to act as a potential reference for government assistance programmes for cancer drugs.

Materials and Methods

Design and Setting

This was a cross-sectional study conducted at two health centres in Malaysia between November 2019 and March 2020. Ampang Hospital, Kuala Lumpur, is the national intervention centre for all haematological conditions, and its haematology expertise has led to the MOH naming it the National Reference Centre (Ministry of Health Malaysia, 2017). This tertiary publicly funded specialist hospital caters to more than 800 patients with CML from at least three neighbouring states, thus serving

approximately half of the patients with CML in the country. Hospital Canselor Tuanku Muhriz, Kuala Lumpur, is one of the four public teaching hospitals in Malaysia. It has more than 1,000 beds and manages approximately 100 patients with CML (Malaysian Medical Resources, 2020).

For this study, patients with CML were recruited via random sampling from the haematological outpatient clinics of Hospital Ampang and Hospital Canselor Tuanku Muhriz. Participation was voluntary and written informed consent was obtained from the patients or the parents/legal caretakers of patients aged <18 years. The inclusion criteria were patient with CML receiving treatment at the aforementioned health centres and at least 1-month treatment with either imatinib or nilotinib but not both. All eligible patients were informed of the study purpose and those who consented to participate were provided with a validated questionnaire in English or Malay based on their preference. We obtained further information from the hospital information system and the patients' medical notes. The study was approved by the ethics committees of the participating health centres and the MOH Medical Research and Ethics Committee (MREC) (NMRR-19-1090-47137 IIR).

Cost Analysis

The total cost of managing CML was calculated from the care provider's perspective. Costing data were obtained from the MOH Casemix MalaysianDRG. The MOH Casemix System was developed as a patient classification tool that groups patients with relatively homogenous resources and clinical characteristics for each group using MalaysianDRG V2 2016 (Pharmacoeconomic guidelines for Malaysia, 2018). The main outputs retrievable from the Executive Information System module include Major Diagnostic Categories, Diagnosis-Related Group (DRG), treatment cost per DRG, Severity of Illness, and Casemix Index (hospital efficiency index) (Pharmacoeconomic guidelines for Malaysia, 2018). To date, a total of 102 government hospitals and medical institutions in all 14 Malaysian states use the casemix system and MalaysianDRG. The casemix system uses the top-down costing approach and consists of two types of costing data: direct and indirect cost. Medication cost was calculated based on the unit price of drug year 2018, which was obtained from the hospital administrations and the pharmaceutical company to acquire both the assisted and unassisted drug cost, respectively. The unassisted or listing cost is the recommended retail price at which the manufacturer recommends that the retailer sell the product. The costs were converted into 2020 US dollars (RM4.20 = USD1.00) (Central Bank of Malaysia, 2020).

Then, both the casemix costing data and medication cost were added to yield the total care provider's cost of CML treatment in Malaysia. To prevent double counting, the drug supply component within the casemix costing data was subtracted prior to determining the total provider treatment cost.

Next, the differences between the cost and outcomes of imatinib and nilotinib treatment for patients with CML were compared using the incremental cost effectiveness ratio (ICER). The ICER is the ratio of the increase in

the cost difference of the two treatments to the increase in the difference of the two outcomes of this study. The gross domestic product (GDP) per capita was used as the cost-effectiveness threshold (CET) as recommended by the World Health Organization (WHO) Commission on Macroeconomics and Health (World Health Organization, 2001). An intervention that is <1 GDP per capita is the most cost-effective CML treatment choice (Adam, 2003; Grosse, 2008). In this study, the CET was the 2019 Malaysian GDP per capita of RM46,450 (USD11,059.52) (Department of Statistics Malaysia, 2019).

Measure of Effectiveness

The study effectiveness or outcome was the quality-adjusted life years (QALYs). The QALYs are the recommended measure of outcome for health technology assessment as they encapsulate the effect of a treatment on a patient's length of life and their health-related quality of life (HRQoL) (National Institute for Health and Clinical Excellence, 2013). QALYs are calculated by multiplying the duration of time spent in a health state by the HRQoL weight (i.e. utility score) associated with that health state. Therefore, the two key elements, HRQoL and survival, are incorporated.

The HRQoL or utility scores were obtained with the EuroQol EQ-5D-5L questionnaire, which is a standardised and recommended health status measurement tool to yield a measure of health and quality of life in clinical and economic appraisals (National Institute for Health and Clinical Excellence, 2013; EuroQol Research Foundation, 2019). The EQ-5D-5L measures five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) (Gudex, 2005). Each health state can be denoted using a five-digit number. The answers for the five domains are transformed to generate a summary score, which indicates the overall utility score. The questionnaire has been validated in Malay (Shafie et al., 2011; Chen et al., 2010) with a Cronbach's alpha of 0.58 and measurement has also been validated for the

Malaysian population (Shafie et al., 2019a, 2019b). Prior permission was obtained from EuroQol for the usage of the EQ-5D forms in this study (registration ID: 30756). The survival life-years of patients with CML was obtained via literature review, as there are a lack of published data on local survival analysis for CML.

Sensitivity Analysis

Sensitivity analysis was performed to resolve uncertainties behind the input parameters and to determine and evaluate the robustness of the outcomes towards variations in the final decision model. A best-, base, and worst-case scenario analysis was performed. Multiway sensitivity analysis was conducted to reflect the best- and worst-case scenarios by applying several circumstances for cost and outcomes, such as drug price variation, outcome variation, and the presence of governmental financial assistance (i.e. assisted vs. unassisted). Statistical analysis was performed using the Statistical Package for the Social Sciences 22 (SPSS Inc.). Cost analysis was performed using Microsoft Excel 365 (Microsoft Corp.).

Results

A total of 221 respondents (response rate: 99.5%) consented to participate in this study. Table 1 lists the respondents' demographic characteristics. More than half were male (56.6%) and 53.4% were Malay. The CML stage at diagnosis was predominantly chronic (89.6%), followed by those in the accelerated stage (8.6%) and blast stage (1.8%). More than half of the participants were imatinib users (68.8%) and 31.8% were nilotinib users. The mean age at diagnosis (n = 221) was 40.87 - 16.45 years (range: 13–81 years). The mean duration of diagnosis was 6.38 - 4.65 years, the mean duration to starting TKI medication was 94.24 - 401.27 days, and the mean utility score was 0.889 - 0.140.

Table 2 illustrates the utility score and life expectancy against the CML treatments. The overall mean utility score

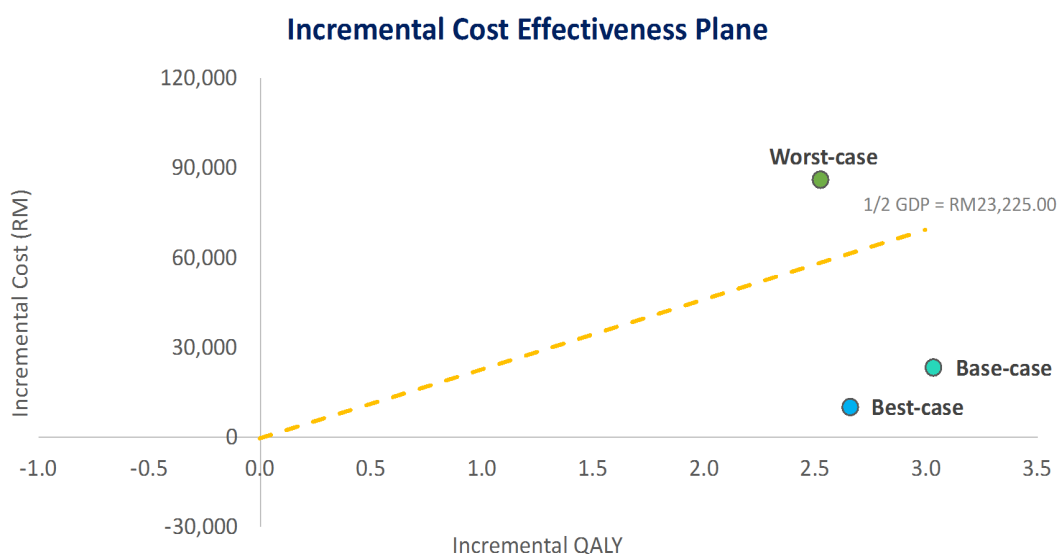


Figure 1. Incremental Cost Effectiveness Plane of Scenario Analysis with 1/2 Gross Domestic Product Per Capita as Cost Effectiveness Threshold

Table 1. Sociodemographic Characteristics of CML Study Population

Variables	Frequency (%)	Mean (range)
Gender		
Male	125 (56.6%)	
Female	96 (43.4%)	
Ethnicity		
Malay	118 (53.4%)	
Chinese	72 (32.6%)	
Indian	29 (13.1%)	
Others	2 (0.9%)	
Phase of CML on diagnosis		
Chronic phase (CP)	198 (89.6%)	
Accelerated phase (AP)	19 (8.6%)	
Blast phase (BP)	4 (1.8%)	
Type of TKI used		
Imatinib	152 (68.8%)	
Nilotinib	69 (31.2%)	
Age on diagnosis (years)		40.9 (13-81)
Duration of diagnosis (years)		6.4 (0-23)
Duration to start TKI (days)		94.2 (0-1802)
Utility score		0.889 (0.116-1)

was 0.887 ± 0.137 for imatinib users and 0.893 ± 0.148 for nilotinib users. The mean life expectancy was 20.15 ± 4.34 for imatinib users and 23.42 ± 4.49 for nilotinib users. Life expectancy data were obtained from a literature review (Botteman et al., 2011; Ovanfors et al., 2011; Snedecor et al., 2012). The QALYs are the product of the HRQoL (i.e. utility score) and survival (i.e. life expectancy). The imatinib users had 17.87 QALYs and the nilotinib users had 20.91 QALYs. There were no significant differences

between the two treatments for both utility score and life expectancy ($p = 0.508$ and $p = 275$, respectively).

Table 3 illustrates the care provider cost for CML treatment in Malaysia both with and without Malaysian governmental financial assistance. Without governmental financial assistance, the average drug cost for each patient with CML per year was USD21,492.86 for imatinib and USD41,921.14 for nilotinib. Aid from MyPAP reduced the average drug cost per patient per year by approximately half at USD12,171.96 and USD17,671.91 for imatinib and nilotinib, respectively. Overall, the presence of MyPAP reduced the care provider cost for CML treatment in Malaysia from USD23,014.40 to USD13,693.51 for imatinib and from USD43,442.69 to USD19,193.45 for nilotinib.

Total cost of treatment by the MOH as the care provider was calculated first by assuming that the fraction of TKI users nationwide was the same as the fraction detected in this study, i.e. 68.8% were imatinib users and 31.2% were nilotinib users based on the current national prevalence of 1,646. The total care provider cost was USD25,366,486.62, where USD15,501,053.32 was spent on imatinib and USD9,865,433.30 on nilotinib.

Table 4 depicts the base case results of the cost-effectiveness analysis from the care provider's perspective. Imatinib was more cost-effective compared to nilotinib for CML treatment as it yielded the lowest cost/QALYs at USD766.29. The ICER of nilotinib compared to imatinib was USD1,809.19.

A scenario sensitivity analysis (Table 5) was performed by applying several cost and outcome circumstances: drug price variation, outcome variation, and presence of governmental financial assistance (assisted vs. unassisted). The imatinib cost/QALYs was valued at USD416.43 in the best-case scenario (lower drug price at extra 15% less, better outcome, assisted provider cost of

Table 2. Utility Score and Life Expectancy against Different CML Treatments

Score	Respondents (n=221)	Imatinib (n=152)	Nilotinib (n=69)	p value
Utility score				
Mean (SD)	0.889 (0.140)	0.887 (0.137)	0.893 (0.148)	0.508 ^a
Life expectancy				
Mean (SD)		20.15 (4.34)	23.42 (4.49)	0.275 ^a
Quality-adjusted life years (QALYs) per patient per year (Utility score*life expectancy)				
		17.87	20.91	

^a, Mann-Whitney U test, significant at $p < 0.05$.

Table 3. Care Provider Cost for CML Treatment in Malaysia

Care provider cost	Governmental financial assistance (MyPAP)			
	Absence		Presence	
	Imatinib	Nilotinib	Imatinib	Nilotinib
Average drug price per CML treatment per patient per year (USD)	21,492.86	41,921.15	12,171.96	17,671.91
Care provider cost for CML treatment per patient per year (USD)	23,014.40	43,442.69	13,693.51	19,193.45
Provider cost of treatment for CML per population per year (RM)	-	-	15,501,053.32	9,865,433.30
Imatinib, n=1,132 (68.8%)				
Nilotinib, n=514 (31.2%)				
Total cost of treatment by Ministry of Health Malaysia as the care provider (USD)			25,366,486.62	

Table 4. Base Case Results of the Cost-Effectiveness Analysis from the Care Provider's Perspective

	Cost (USD)	QALYs	Cost/QALYs (USD)	ICER
Imatinib	13,693.51	17.87	766.29	
Nilotinib	19,193.45	20.91	917.91	1,809.19

treatment), USD766.29 in the base case scenario (average drug price, average outcome, assisted provider cost of treatment), and USD1,447.33 in the worst-case scenario (undiscounted drug price, reduced outcome, unassisted provider cost of treatment). The cost/QALY for nilotinib was valued at USD464.29 in the best-case scenario, USD917.91 in the base-case scenario, and USD2,412.56 in the worst-case scenario.

Figure 1 illustrates the incremental cost-effectiveness plane of scenario analysis with the 50% GDP per capita as the CET. All three scenarios demonstrated positive incremental costs and incremental QALYs. Nonetheless, only best- and base case scenarios were below the CET.

Discussion

Good health cannot be achieved without access to pharmaceutical products. Lack of access to medicines is a health inequality that is of global concern, especially in developing countries. The WHO recommends ensuring that all people and communities receive the quality services they need and are protected from health threats without financial hardship (World Health Organization, 2017). This includes the full range of critical affordable health services, from prevention, diagnosis, recovery, and palliative care to health promotion. Regrettably, approximately 100 million people worldwide are in "extreme poverty" due to overpaid healthcare costs (World Health Organization, 2017). Nonetheless, health access inequality is both preventable and solvable. With better healthcare access following progress devoted to the poor and rural populations via fairer and more equitable financing, health inequalities have been decreasing in the past 20 years (Victora et al., 2017).

CML is a health condition that requires lifelong commitment, which is often both physical and mentally draining, time-consuming, and financially burdensome. TKI treatment was instrumental in changing the status of CML from a lethal to chronic disease. Prior to the availability of TKI treatment, the average survival of patients with CML was only 5 years (National Comprehensive Cancer Network, 2018). TKI offer potential long-term disease control or even a cure for patients with CML who adhere to the therapy (Dalziel et al., 2004; Druker et al., 2006; Reed et al., 2004; Rochau, Kluibenschaedl, et al., 2015). Unfortunately, TKI are one of the most expensive outpatient drugs available and the price is increasing every year (Chhatwal et al., 2015; Sandmann et al., 2013). Funding issues are the main concern in the choice of medication used for CML worldwide, including Malaysia. Without financial assistance, very few patients can afford any type of TKI, hence low-income countries still use other types of

Table 5. Scenario Sensitivity Analysis

Treatment	Scenario (Cost/QALYs) (USD)		
	Best ^a	Base ^b	Worst ^c
Imatinib	416.43	766.29	1,447.33
Nilotinib	464.29	917.91	2,412.56
ICER	916.66	1,809.19	8,074.42

^a Best-case scenario, All patients with CML using either imatinib or nilotinib, lowest drug price, same outcome (QALYs), assisted provider cost of treatment; ^b Base case scenario, Proportion of TKI users (imatinib, 68.8%; nilotinib, 31.2%), average drug price, same outcome (QALYs), assisted provider cost of treatment; ^c Worst-case scenario, All patients with CML using either imatinib or nilotinib, highest drug price, reduced outcome (QALYs), unassisted provider cost of treatment.

medication, such as interferon, which yield a much poorer outcome for treating CML (Au et al., 2009).

The present study is the first economic evaluation to pioneer assessment of the cost-effectiveness of CML treatment in Malaysia. We determined that nilotinib has a higher drug price than imatinib and a better utility score and life expectancy; therefore, it has better QALYs. Nilotinib is a second-generation TKI that many studies have reported as being the superior TKI to imatinib, where it causes fewer adverse effects and with an earlier and deeper molecular response (Kantarjian et al., 2011; Larson et al., 2012; Wang et al., 2015). However, nilotinib is costlier. Moreover, nilotinib did not demonstrate a statistically significant difference when compared to imatinib despite the better utility score. Furthermore, the life expectancy between both medications was not statistically significantly different. It is presumed that spending more on nilotinib is not worthwhile when the incremental outcome is not significant.

Previous studies on the cost-effectiveness of CML treatment have yielded mixed results. Some studies concluded that imatinib is more cost-effective than nilotinib (Rochau et al., 2015a, 2015b; Li et al., 2018). Imatinib would become more cost-effective when generic imatinib becomes available, causing its price to decline; subsequently, it would become more cost-effective compared to nilotinib (Padula et al., 2016). Nonetheless, others agreed that nilotinib is highly cost-effective when compared to imatinib (Romero et al., 2014). (Mildred et al., 2012) reported that nilotinib improved survival and QALYs compared to standard treatment of first-line imatinib and is likely to be a cost-effective use of care provider resources.

An issue in the present study is that the unbalanced proportion of imatinib and nilotinib users. Approximately two-thirds (68.8%) of patients with CML were imatinib users as compared to the 31.2% of nilotinib users. This may be due to the fact that MyPAP allocates more numbers of the cheaper drug so that more patients can access the medication. This drug distribution inequality in the patient assistance programme therefore caused less allocation of the more effective nilotinib. If all allocations were assigned to the most effective drug, it would yield better and higher outcome values, which would result in nilotinib becoming more cost-effective compared to imatinib, as determined by the best-case scenario analysis in our study.

Implementing national insurance coverage may overcome the issue of drug distribution inequality as it enables resource pooling to subsidise healthcare costs, thus providing the best medical care without financial strain. Countries such as South Korea, Taiwan, and Hong Kong implement national insurance schemes that cover, or at least present the option, to cover for cancer drugs (Au et al., 2009). Since TKI were introduced, insurance plans have implemented many policies to control prescription drug costs, including raising co-payments and increasing the use of co-insurance. Whereas countries such as Singapore have government-operated savings and medical insurance programmes apart from private health insurance schemes, the schemes all have the same aim of providing high-quality healthcare at a low cost.

Nonetheless, there remains a need to reduce the overall cost of managing CML. MyPAP aids the MOH as the care provider to reduce the cost of managing CML by almost half. Nonetheless, MyPAP is not ideal and its sustainability is doubtful. Spending more than USD20,000,000 annually to manage CML nationwide imposes a substantial financial burden on the country, where an enormous portion of the expenditure comes from drug purchasing. Unfortunately, the presence of a patient assistance programme prevents the purchase of alternative drugs, such as generic imatinib, that demonstrate the same efficiency but at a much lower price (Abou Dalle et al., 2019; Entasoltan et al., 2017; Lejniece et al., 2017). Additionally, the collaboration of various ministries and private agencies may reduce this financial burden by providing appropriate and affordable services specifically to patients with CML. To increase awareness of more affordable cancer drug options and for patients with cancer to understand their drug needs and financially viable drug treatment options, more patient support activities should be organised, such as patient congress, educational patient camps, patient education workshops, patient newsletters, community events, and health exhibitions (Ching, 2011).

Another issue is that the drug allocation quantities should be improved. Under the patient assistance programme, drug allocation numbers by the pharmaceutical company are limited. However, we determined that the list of company-sponsored patients is limited and patients are on waiting lists for up to several months before they can access the medication. This drug distribution inequality is unacceptable as patients are forced to wait to access the medication deemed effective for treating their condition and prolonging their life.

This study has several limitations. First, the respondents were recruited from a limited number of healthcare facilities and there was limited coverage of specific Malaysian regions. Hence, the data may not be representative of all CML cases in Malaysia. Nevertheless, the data provided meaningful insight into drug purchasing for managing CML from the perspective of the MOH as the care provider. Second, the COVID-19 pandemic affected the data collection flow whereby patients with CML are considered a high-risk community, which led to the closure of outpatient clinics. It would be beneficial to perform an economic evaluation study from the societal perspective that is more extensive, relevant, and provides

a better understanding of the financial burden of treatment among patients with CML. In addition, a budget impact analysis that estimates the financial consequences and effect of adopting nilotinib as a new treatment for patients with CML would be advantageous.

Ultimately, the question of how medication access for patients with CML can be improved should be highlighted. The pandemic era has invariably affected the economic status and finances of the public. Therefore, the availability and continuation of patient assistance programmes, such as MyPAP, are necessary to ensure that the appropriate treatments are accessible and affordable. Achieving universal health coverage requires enormous efforts, where all societal levels must cooperate to implement it. A more transparent and sustainable system for the healthcare sector should be considered, where a National Social Health Insurance (NSHI) and Voluntary Health Insurance (VHI) scheme should be considered.

In conclusion, nilotinib has a higher drug price than imatinib, yet yields better life expectancy, utility score, and QALYs. Overall, imatinib is more cost-effective compared to nilotinib for treating CML in Malaysia from the care provider's perspective. Nonetheless, the ICER of nilotinib to imatinib suggested that nilotinib is cost-effective when compared to the national GDP per capita. This study suggests the importance of funding assistance for patients with CML, particularly in ensuring that the appropriate treatments are accessible and affordable. Nonetheless, the drug distribution inequality as a result of the patient assistance programme should be addressed to establish an effective, efficient, sustainable, and equitable health expenditure for treating CML in Malaysia.

Author Contributions Statement

SEWP: Study inception, study design, and liaising; critical revision of the manuscript for important intellectual content; supervisory role of study progress; administrative and material support. EMS: Conception and design; data acquisition, analysis, and interpretation; drafting the manuscript and statistical analysis. ANA: Study progress monitoring; manuscript revision for important intellectual content. NRT: Data acquisition; manuscript revision for important intellectual content. JS: Data acquisition; manuscript revision for important intellectual content.

Acknowledgements

We thank the Director General of Health Malaysia for his permission to publish this article. We also thank all patients who participated in this study and acknowledge the essential contributions of the Ampang Hospital and Hospital Canselor Tuanku Muhriz Departments of Haematology for their support and cooperation in this study.

Ethics Approval and Consent to Participate

Ethical approval for this study was obtained from the MOH MREC (NMRR-19-1090-47137 IIR).

Availability of Data

All acquired data are available within the article.

Conflict of Interest

Authors declare that they have no conflicts of interest.

References

- Abou Dalle I, Kantarjian H, Burger J, et al (2019). Efficacy and safety of generic imatinib after switching from original imatinib in patients treated for chronic myeloid leukemia in the United States. *Cancer Med*, **8**, 6559–65.
- Adam T (2003). Making choices in health: WHO guide to cost-effectiveness analysis. World Health Organization, Geneva, 312 p.
- Au WY, Caguioa PB, Chuah C, et al. (2009). Chronic myeloid leukemia in Asia. *Int J Hematol*, **89**, 14–23.
- Besa E, Buehler B, Markman M, Sacher RKK (2014). Chronic myelogenous leukemia treatment & management. <https://emedicine.medscape.com/article/199425-overview#aw2aab6b6b8> (Accessed 18-Apr-2021)
- Botteman M, Stephens J, Snedecor SJ, et al (2011). Long-term estimate of quality-adjusted life expectancy for nilotinib and imatinib as first-line treatment for newly diagnosed patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in the chronic phase (CML-CP). *J Clin Oncol*, **29**, 6570.
- Central Bank of Malaysia (2020). Exchange Rates. <https://www.bnm.gov.my/exchange-rates>. (Accessed 1-June-2021)
- Chhatwal J, Mathisen M and Kantarjian H (2015). Are high drug prices for hematologic malignancies justified? A critical analysis. *Cancer*, **121**, 3372–9.
- Ching OM (2011). Malaysia patient assistance program. <https://www.cmladvocates.net/download/cml-horizons-conferences/rising-sun-2011/46-rs-2011-show-and-tell-malaysian-patient-assistance-program-mei-ching/file>. (Accessed 30-Oct-2018)
- Dalziel K, Round A, Stein K, et al. (2004). Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. *Health Technol Asses*, **8**, 1-120.
- Department of Statistics Malaysia (2019). Socioeconomics Report. Department of Statistics, Malaysia.
- Druker BJ, Guilhot F, O'Brien SG, et al (2006). Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*, **355**, 2408–17.
- Du J, Yang X, Chen M, Wang Z (2019). Socioeconomic determinants of out-of-pocket pharmaceutical expenditure among middle-aged and elderly adults based on the China Health and Retirement Longitudinal Survey. *BMJ Open*, **9**, 24936.
- EuroQol Research Foundation (2019). EQ-5D-5L User Guide. <https://EuroQol.org/publications/user-guides>. (Accessed 1-Nov-2020)
- Entasoltan B, Bekadja MA, Touhami H, et al. (2017). Outcome of frontline treatment with “generic” imatinib in adult patients with chronic myeloid leukemia in Algerian population: A multicenter study. *Mediterr J Hematol Infect Dis*, **9**, e2017062.
- Grosse SD (2008). Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY threshold. *Expert Rev Pharm Out*, **8**, 165–78.
- Gudex C (2005). The descriptive system of the EuroQol Instrument BT - EQ-5D concepts and methods: A developmental history. Eds Kind P, Brooks R, and Rabin R. Springer, Dordrecht, pp 19–27.
- Kantarjian HM, Hochhaus A, Saglio G, et al (2011). Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. *Lancet Oncol*, **12**, 841–51.
- Kong Y-C, Kimman M, Subramaniam S, et al. (2010). Out-of-pocket payments for complementary medicine following cancer and the effect on financial outcomes in middle-income countries in southeast Asia: a prospective cohort study. *Lancet Glob Heal*, **10**, e416–28.
- Kim D-W, Banavali SD, Bunworasate U, et al. (2010). Chronic myeloid leukemia in the Asia-Pacific region: Current practice, challenges and opportunities in the targeted therapy era. *Leuk Res*, **34**, 1459–71.
- Kuan JW, Melaine Michael S (2018). The epidemiology of chronic myeloid leukaemia in southern Sarawak, Borneo Island. *Med J Malaysia*, **73**, 78-85.
- Larson RA, Hochhaus A, Hughes TP, et al. (2012). Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. *Leukemia*, **26**, 2197–203.
- Lejniece S, Udre I, Rivkina A (2017). Generic imatinib in the treatment of chronic myeloid leukemia: two years' experience in Latvia. *Exp Oncol*, **39**, 151–4.
- Li N, Zheng B, Cai H-F, et al (2018). Cost effectiveness of imatinib, dasatinib, and nilotinib as first-line treatment for chronic-phase chronic myeloid leukemia in China. *Clin Drug Invest*, **38**, 79–86.
- Lu CY, Lupton C, Rakowsky S, et al (2015). Patient access schemes in Asia-pacific markets: current experience and future potential. *J Pharm Policy Pract*, **8**, 6.
- Lu Y, Hernandez P, Abegunde D, Edejer T (2011). The world medicines situation. World Health Organization, Geneva, 145 p.
- Malaysian Medical Resources (2020). Public Hospitals. <https://new.medicine.com.my/government/hospitals/?cns=WP&Kuala&Lumpur> (Accessed 31-Aug-2020).
- Milani B and Scholten W (2011). The World Medicines Situation. Access To Controlled Medicines. World Health Organization, Geneva, 19 p.
- Mildred M, Ward S, Squires H, et al (2012). Cost-effectiveness analysis of nilotinib versus imatinib for the treatment of chronic phase Philadelphia chromosome positive chronic myeloid leukaemia. In: 17th Congress of EHA, 14-17 June 2012, Amsterdam, The Netherlands.
- Ministry of Health Malaysia (2017). Ampang Hospital Department of Haematology. <https://hampg.moh.gov.my/index.php/informasi/senarai-jabatan-perkhidmatan/klinikal/jabatan-hematologi>. (Accessed 21-Jan-2021)
- National Comprehensive Cancer Network (2018). Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. (Accessed 23-Apr-2021)
- National Institute for Health and Clinical Excellence (2013). Guide to the Methods of Technology Appraisal. <https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781>. (Accessed 20-Oct-2018)
- Ovanfors A, Stephens J, Snedecor SJ, et al (2011). Cost-effectiveness of nilotinib versus imatinib as first-line treatment for newly diagnosed patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in the chronic phase (CML-CP): Swedish perspective. *J Clin Oncol*, **29**, 6572.
- Padula WV, Larson RA, Dusetzina SB, et al (2016). Cost-effectiveness of Tyrosine Kinase Inhibitor Treatment

- Strategies for Chronic Myeloid Leukemia in Chronic Phase After Generic Entry of Imatinib in the United States. *J Natl Cancer Inst*, **108**, djw003.
- Pharmacoeconomic guidelines for Malaysia (2018). <https://www.pharmacy.gov.my/v2/sites/default/files/document-upload/pharmacoeconomic-guidelines-malaysia-malaysia-second-edition-2019-final-page-adjustment.pdf>. (Accessed 20-Oct-2019)
- Reed SD, Anstrom KJ, Ludmer JA, et al. (2004). Cost-effectiveness of imatinib versus interferon-alpha plus low-dose cytarabine for patients with newly diagnosed chronic-phase chronic myeloid leukemia. *Cancer*, **101**, 2574–83.
- Rochau U, Sroczynski G, Wolf D, et al. (2015a). Cost-effectiveness of the sequential application of tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia. *Leuk Lymphoma*, **56**, 2315–25.
- Rochau U, Kluibenschaedl M, Stenehjem D, et al. (2015b). Effectiveness and cost-effectiveness of sequential treatment of patients with chronic myeloid leukemia in the United States: A Decision Analysis. *Leuk Res Treatment*, **2015**, 982395.
- Romero M, Chávez D, De Los Ríos M, et al. (2014). Cost-effectiveness of nilotinib, dasatinib and imatinib as first-line treatment for chronic myeloid leukemia in Colombia, 2012. *Biomedica*, **34**, 48–59.
- Sandmann FG, Franken MG, Steenhoek A, et al. (2013). Do reassessments reduce the uncertainty of decision making? Reviewing reimbursement reports and economic evaluations of three expensive drugs over time. *Health Policy*, **112**, 285–96.
- Shafie AA, Hassali MA and Liau SY (2011). A cross-sectional validation study of EQ-5D among the Malaysian adult population. *Qual Life Res*, **20**, 593–600.
- Shafie AA, Vasan Thakumar A, Lim CJ, Luo N, et al. (2019a). EQ-5D-5L Valuation for the Malaysian Population. *Pharmaco Economics*, **37**, 715–25.
- Shafie AA, Vasan Thakumar A, Lim CJ, Luo N (2019b). Psychometric performance assessment of Malay and Malaysian English version of EQ-5D-5L in the Malaysian population. *Qual Life Res*, **28**, 153–62.
- Snedecor SJ, Ji X, Magestro M, et al (2012). Estimating Long-Term Life Expectancy in Philadelphia Chromosome Positive (Ph+) Chronic Phase Chronic Myeloid Leukemia (CML-CP): Results of A Microsimulation Model. *Blood*, **120**, 4441.
- Victora CG, Barros AJD, França GVA, et al. (2017). The contribution of poor and rural populations to national trends in reproductive, maternal, newborn, and child health coverage: analyses of cross-sectional surveys from 64 countries. *Lancet Glob Health*, **5**, e402–7.
- Wang Jianxiang, Shen Z-X, Saglio G, et al (2015). Phase 3 study of nilotinib vs imatinib in Chinese patients with newly diagnosed chronic myeloid leukemia in chronic phase: ENESTchina. *Blood*, **125**, 2771–8.
- Won-Sun C, Shanthi V, Geeta AGS (2010). Psychometric properties of the Malay version of the EQ-5D in Malaysia. *SEGi Rev*, **3**, 45–51.
- World Health Organization (2001). Macroeconomics and health: Investing in health for economic development: executive summary. World Health Organization, Geneva, 20 p.
- World Health Organization (2017). Universal health coverage (UHC). https://www.who.int/health-topics/universal-health-coverage#tab=tab_1. (Accessed 14-Oct-2018)



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