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An Evaluation of Medication Adherence to Tyrosine Kinase Inhibitors Among Chronic Myeloid Leukemia Patients Underwent Medication Therapy Adherence Clinic in a Malaysian Tertiary Hospital

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ABSTRACT

Introduction: The treatment of chronic phase chronic myeloid leukemia (CML) has changed dramatically within the last two decades with the emergence of tyrosine kinase inhibitors (TKI). Treatment adherence to long-term TKI is pivotal to improving clinical outcomes in CML patients. **Objective:** To evaluate medication adherence to TKI and contributory variables affecting medication adherence among CML patients underwent Medication Therapy Adherence Clinic (MTAC). **Method:** This was a single-centre cross-sectional study conducted between January and December 2021. Malaysia Medication Adherence Assessment Tool (MyMAAT) was employed to assess medication adherence among CML MTAC patients. Descriptive statistics were used to summarise adherence information. Fisher's exact test was performed to examine relationships between TKI adherence level, demographic and clinical variables. **Result:** Records of 41 patients (61% male, 39% female) at average age of 51 years old (range = 26 to 75) were analysed. They had been taking imatinib (48.8%) and nilotinib (51.2%) for an average of 6.3 years (range = 17 days to 18 years). Overall, 90% of the patients were adherent (MyMAAT score ≥ 54) to their TKI treatment (95% of patients on imatinib, 86% of patients on nilotinib). Medication adherence to TKI was not significantly influenced by demographic variables (*i.e.* age, gender) and clinical variables (*i.e.* years on TKI, number of TKI pills per day, type of TKI therapy). **Conclusion:** Majority of the CML MTAC patients (90%) were adherent to their TKI therapy. Adherence scores were not affected by the demographics and clinical variables investigated in this study. This affirms the role of pharmacists in implementing an individualised and comprehensive intervention strategy.

INTRODUCTION

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disease characterised by the presence of the Philadelphia chromosome and its fusion gene, BCR-ABL. BCL-ABL oncogene codes for an oncoprotein which in turn stimulates myeloid cells proliferation [1]. According to the Malaysian National Cancer Registry Report 2007–2011, there were 573 CML patients in Malaysia at the time of reporting, which accounts for 12.5% of total leukaemia cases in the country [2].

The advent of tyrosine kinase inhibitor (TKI) targeting the BCL-ABL oncoprotein has transformed the treatment landscape of this previously fatal disease by augmenting disease response and reducing treatment-related morbidity.

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Imatinib, nilotinib and ponatinib are the TKIs currently registered in Malaysia. The majority of CML patients in Malaysia gain access to TKI therapy under the Malaysia Patient Assistance Programme (MYPAP), a public-private partnership launched by a pharmaceutical company in collaboration with the Ministry of Health [3].

Although treatment outcome for CML patients has markedly improved owing to the emergence of these oral targeted therapies, the suboptimal response is still reported in a subgroup of patients [4]. Apart from the development of genetic mutations and poor access to medication, poor adherence to TKI is also one of the factors contributing to suboptimal response and treatment failure [5][6].

Medication adherence can be defined as the extent to which the patient's actions meet the prescriber's recommendations or expectations [7]. For long-term conditions, it is estimated that 30-50% of prescribed medicines are not taken as recommended. A meta-analysis found that between a quarter to one-third of CML patients were not adhering to their TKI therapy [8].

The CML Medication Therapy Adherence Clinic (MTAC) is a service provided by the Pharmacy Department of Hospital Canselor Tuanku Muhriz (HCTM UKM). Interviews, individualised counselling, and medication adherence assessment are carried out by pharmacists during MTAC to optimise TKI therapy and enhance patients' adherence to prescribed treatment. All CML MTAC pharmacists underwent one training session on theory and one practical session in an actual clinic setting.

To date, there has been a lack of local studies focusing on medication adherence among CML patients treated with TKIs. This study aims to evaluate medication adherence to TKI among CML MTAC patients and explore the possible variables associated with TKI adherence in a tertiary hospital in Malaysia.

MATERIAL AND METHOD

Study Design and Population

This cross-sectional study included adult patients who attended CML MTAC between January 2021 to December 2021 (totalling 16 sessions) conducted by 15 pharmacists on a rotation basis. The CML MTAC is held fortnightly in conjunction with CML outpatient clinics. Patients recruited are diagnosed with chronic- or accelerated-phase CML, are on active treatment with either imatinib or nilotinib for ≥ 2 weeks and can arrive 30 minutes earlier than their assigned time for their doctor's appointments. Total population sampling was employed. As part of the MTAC workflow, patients' medication adherence was evaluated using the Malaysia Medication Adherence Assessment Tool (MyMAAT), a 12-item, bilingual (English and Malay), a self-administered questionnaire consisting of 5 constructs. [9] Each question is a 5-point Likert item from "strongly disagree" to "strongly agree". The MyMAAT score was the sum of the marks for the individual items ranging between 12 and 60. Medication adherence was categorised as good adherence (MyMAAT score ≥54) and moderate/poor adherence (MyMAAT score <54). The scores were documented manually on the patient's pharmaceutical care form.

The sample size was calculated using Cochran's equation. This study requires 41 samples to represent the population size of 45 at a 5% confidence interval with an alpha of 0.05, a power of 0.8 and an estimated proportion of 0.5.

Data Analysis

Statistical analysis was performed using SPSS® (version 26). Power and sample size calculations were performed using G*Power 3.1.9.4. the demographic characteristics of the patients (age and gender) were obtained from the hospital information system. Clinical characteristics (type of TKI, dose and frequency, TKI pills per day, duration on TKI treatment) were retrieved from the hospital's e-prescribing system. Descriptive statistics were used to summarise the adherence information retrieved from pharmaceutical care forms. Medication adherence was assessed during every MTAC visit. If there were two MyMAAT scores available in our records for the same patient within the study period, the latest score was used for data analysis. Hence, the medication adherence measured represented the patient's adherence after at least one session of MTAC. Fisher's exact test was employed to examine the association between patients' demographic and clinical variables with medication adherence towards TKI therapy. A two-tailed p-value of <0.05 was considered as statistically significant.

Post-hoc Analysis

The internal consistency of MyMAAT was tested using Cronbach's alpha (Cronbach's alpha = 0.787). The required sample size for Fisher's exact test to achieve the power of 0.8, with α=0.05 was 808 (404 per group).

RESULT

Of the 45 patient records retrieved from the CML MTAC, 41 patients were included in the final analysis. A total of 4 patients were excluded due to incomplete data (n=3) and funding issues leading to interruption of drug supply (n=1).

Adherence to TKI treatment

Overall, 90% (n=37) of the study population showed good adherence to TKI treatment. As shown in Figure 1, amongst patients receiving imatinib (n=20) and nilotinib (n=21), 95% and 86% of them demonstrated good medication adherence, respectively.

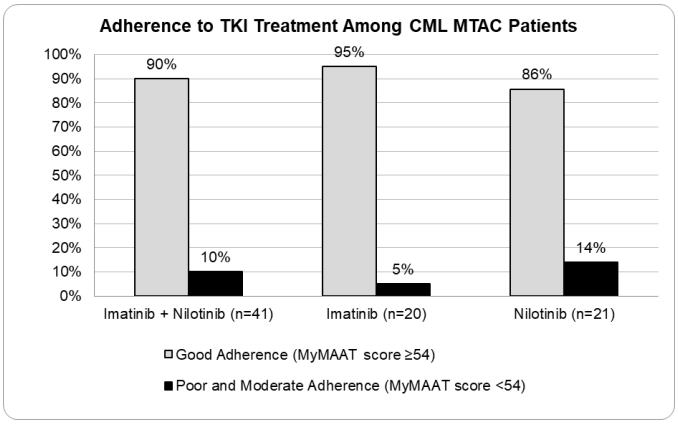

Figure I. Adherence to TKI Treatment Among CML MTAC Patients

Demographic and Clinical Variables

Table I shows the demographic and clinical variables of the 41 patients analysed. 41.5% (n=17) of the patients were elderly, aged at least 60 years old. 82.4% (n=14) of the elderly patients showed good adherence. The number of male patients recruited (n=25, 61.0%) was higher than that of female patients (n=16, 39.0%). A greater proportion of males (n=24, 96.0%) showed good adherence compared to their female counterparts (n=13, 81.2%). The majority of the patients (n=31, 75.6%) had been on TKI treatment for less than 10 years with 87.1% (n=27) of them showing a good adherence. Meanwhile, 100% (n=10) of patients on TKI treatment for more than 10 years demonstrated good adherence. Most of the patients (n=25, 61.0%) were taking only one to two tablets per day for their CML treatment with 84% (n=21) of them demonstrating good adherence. 39% (n=16) of the study population were taking three to four tablets per day and all of them showed good adherence.

Amongst all the demographic and clinical variables analysed, there was no significant difference (p-value > 0.05) observed across the subjects in terms of adherence towards TKI treatment.

Table I: Association between demographic and clinical characteristics of patients (n=41) with adherence to TKI treatment

Characteristic	Frequency	Percentage	Adherence Level Frequency (Percentage)		p-value
			Good	Moderate/Poor	
Age*	Mean = 51	Range = 26-75			
<60 years	24	58.5	23 (95.8)	1 (4.2)	0.29
≥60 years	17	41.5	14 (82.4)	3 (17.6)	
Gender					
Male	25	61.0	24 (96.0)	1 (4.0)	0.28
Female	16	39.0	13 (81.2)	3 (18.8)	
Years on TKI Treatment*	Mean = 6.3	Range=17days-18 years			
<10 years	31	75.6	27 (87.1)	4 (12.9)	0.56
≥10 years	10	24.4	10 (100.0)	0 (0.0)	
Type of TKI					
Imatinib	20	48.8	19 (95.0)	1 (5.0)	0.61
Nilotinib	21	51.2	18 (85.7)	3 (14.3)	
Dosing Frequency					
Once a day	20	48.8	19 (95.0)	1 (5.0)	0.61
Twice a day	21	51.2	18 (85.7)	3 (14.3)	
TKI Pill(s) per Day					
1-2	25	61.0	21 (84.0)	4 (16.0)	0.14
3-4	16	39.0	16 (100.0)	0 (0.0)	

***at the time of adherence evaluation**
Good adherence (MyMAAT score ≥54), Moderate/Poor adherence (MyMAAT score <54)

DISCUSSION

The substantially higher number of male CML patients recruited in the study is consistent with the male/female ratio of 1.2–1.7 demonstrated in epidemiology studies. [10] The similar amount of imatinib and nilotinib patients recruited is in congruence with the MYPAP allocation of 1:1 for these TKIs at our institution.

The study population demonstrated relatively better adherence towards TKI treatment as a whole compared to another local study conducted among CML patients. [11] Patients on imatinib treatment showed higher medication adherence probably due to a better tolerance profile. Compared to other TKIs, imatinib showed better tolerability due to fewer drug-related adverse effects and its convenience with once-daily dosing [12]. More optimal adherence among the patients in this study might be the effect of participation in CML MTAC. All patients in this study were active MTAC patients who have attended at least 1 session of MTAC prior to data collection. The beneficial effects of medication management services on TKI adherence and clinical outcome were demonstrated in a number of studies. [13] A randomised controlled trial done in two Malaysian hospitals found that pharmacist-led interventions resulted in significantly better medication adherence and faster achievement of major molecular response, especially during the early months after treatment initiation. [14]

TKI-specific clinical factors like the number of TKI pills per day and dosing frequency were not associated with TKI adherence in this study. TKI adherence can be affected by the total pill burden per day contributed by medications used to treat other concomitant diseases. Concomitant drug burden was identified by Efficace F *et al.* to be one of the predictors of treatment non-adherence in patients on long-term imatinib therapy. [15] Another group of predictors which was not explored in the present study is drug-related issues like sideeffects of TKI. Lee PM *et al.* found a significant association between nausea and vomiting experienced by CML patients and patient adherence in a Malaysian hospital. [11]

MyMAAT is a relatively new tool developed to assess medication adherence and validated among the diabetic population (Cronbach alpha = 0.910). [9] It is widely utilised by pharmacists in Malaysian hospitals for various patient populations and is included in various MTAC protocols. [16] [17] To the best of our knowledge, this is the first study that utilises MyMAAT to assess medication adherence in CML patients. Apart from assessing overall adherence based on the total score, pharmacists can identify domains in which the patients showed suboptimal scoring and provide follow-up counselling and/or education tailored to individual patients. Compared to the most widely used MMAS-8 which involves a fixed charge per form used, MyMAAT is more economical. [18] Other commonly used adherence assessment methods like pill count and medication possession ratio require patients to bring their medications to every clinic visit and have the availability of complete dispensing records respectively. These are less convenient to be employed for day-to-day practice for MTAC service.

A pilot study to test the feasibility of MyMAAT in CML patients was not carried out as data was collected retrospectively from MTAC records where MyMAAT was already incorporated into the clinic workflow. Post-hoc reliability analysis shows acceptable internal consistency of MyMAAT (Cronbach alpha = 0.787) in our study population. Validation of the tool in CML population could be done in future studies with a larger sample size.

One of the limitations of this study is the small sample size as it was a single-centre study targeting a relatively uncommon disease. The study population consisted of patients who attended MTAC throughout 2021 during the coronavirus pandemic. They might be more health-conscious and more adherent to their treatment. This study also did not include patients who defaulted clinic appointments. The final sample size of 41 was able to represent the study population and reflect the overall medication adherence level. However, post-hoc analysis demonstrated that the sample size was inadequate to achieve desirable power to detect the association of different variables and medication adherence (if any).

Despite attending regular physician consultations and counselling sessions by pharmacists, 10% of the patients showed suboptimal adherence which has no association with certain demographics and clinical variables. This highlights other factors or gaps in service that require further approaches. Further studies could be done prospectively to explore other factors like socioeconomic status, access to medication, drug-related issues, education level as well as concomitant diseases and medications that might influence TKI adherence.

CONCLUSION

Majority of the CML MTAC patients (90%) were adherent to their long-term TKI treatment. This affirms the role of pharmacists in implementing an individualised and comprehensive intervention strategy to optimise TKI treatment and resolve drug-related issues during MTAC service. Adherence scores were not affected by the demographics and clinical variables investigated in this study. Future studies involving a larger sample size are warranted to identify factors associated with adherence to TKI therapy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCE

[1] National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia V.2.2022.2021 [cited 2022 Feb 5] Available from: https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.

[2] Azizah Ab M NSIT, Noor Hashimah A, Asmah Z.A, Mastulu W. Malaysian National Cancer Registry Report 2011 [cited 2022 Feb 5] Available from: https://www.crc.gov.my/wp-content/uploads/documents/report/MNCRRepor2007-2011.pdf.

[3] Ministry of Health Malaysia. National Strategic Plan for Cancer Control Programme 2016-2020, 1st ed. [cited 2022 Feb 5] Available from: https://www.iccp-portal.org/plans/national-strategic-plan-cancer-control-programme

[4] Deininger M, O'Brien SG, Guilhot F, Goldman JM, Hochhaus A, Hughes TP, *et al.* International randomized study of interferon vs STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. Blood. 2009;114(22):1126. https://doi.org/10.1182/blood.V114.22.1126.1126

[5] Ibrahim AR, Eliasson L, Apperley JF, Milojkovic D, Bua M, Szydlo R, *et al.* Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. Blood. 2011;117(14):3733–3736. https://doi.org/10.1182/blood-2010-10-309807

[6] Marin D, Bazeos A, Mahon FX, Eliasson L, Milojkovic D, Apperley JF, *et al.* Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J Clin Oncol. 2010;28(14):2381–2388. https://doi.org/10.1200/JCO.2009.26.3087

[7] Wiffen P, Mitchell M, Snelling M, Stoner N. Oxford Handbook of Clinical Pharmacy, 3rd ed. Oxford: Oxford University Press; 2017. 2p.

[8] Alrabiah Z, Alhossan A, Yun S, MacDonald K, Abraham I. Adherence to tyrosine kinase inhibitor therapy in patients with chronic myeloid leukemia: meta-analyses of prevalence rates by measurement method. Blood. 2016;128(22):3610. https://doi.org/10.1182/blood.V128.22.3610.3610

[9] Hatah E, Rahim N, Makmor-Bakry M, Mohamed Shah N, Mohamad N, Ahmad M, *et al.* Development and validation of Malaysia Medication Adherence Assessment Tool (MyMAAT) for diabetic patients. PLoS ONE 2020;15(11): e0241909. https://doi.org/10.1371/journal.pone.0241909

[10] Lin Q, Mao L, Shao L, Zhu L, Han Q, Zhu H, *et al.* Global, Regional, and National Burden of Chronic Myeloid Leukemia, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017. Front Oncol. 2020 Dec 15;10:580759. https://doi.org/10.3389/fonc.2020.580759

[11] Lee PM, Chang CT, Yusoff ZM. Adherence to tyrosine kinase inhibitors among adult chronic myeloid leukemia patients in a Malaysia hospital. Int J Clin Pharm. 2021;43(1):46–54. https://doi.org/10.1007/s11096-020-01070-9

[12] Tang L, Zhang H, Peng Yz, Li Cg, Jiang Hw, Xu M, *et al.* Comparative efficacy and tolerability of front-line treatments for newly diagnosed chronic-phase chronic myeloid leukemia: an update network meta-analysis. BMC Cancer. 2019;19:849. https://doi.org/10.1186/s12885-019-6039-9

[13] Tan BK, Bee PC, Chua SS, Chen LC. Monitoring and Improving Adherence to Tyrosine Kinase Inhibitors in Patients with Chronic Myeloid Leukemia: A Systematic Review. Patient Prefer Adherence. 2021 Nov 18;15:2563-2575. https://doi.org/10.2147/PPA.S269355.

[14] Tan BK, Chua SS, Chen LC, Chang KM, Balashanker S, Bee PC. Efficacy of a medication management service in improving adherence to tyrosine kinase inhibitors and clinical outcomes of patients with chronic myeloid leukaemia: a randomised controlled trial. Sup Care Cancer. 2020;28(7):3237–3247. https://doi.org/10.1007/s00520-019-05133-0

[15] Efficace F, Baccarani M, Rosti G, Cottone F, Castagnetti F, Breccia M, *et al.* Investigating factors associated with adherence behaviour in patients with chronic myeloid leukemia: an observational patient-centered outcome study. British Journal of Cancer. 2012 Sep 4;107(6):904–909. https://doi.org/10.1038/bjc.2012.348.

[16] Ministry of Health Malaysia. Pharmacy Information System (PhIS) and Clinic Pharmacy System (CPS): User Manual Medication Therapy Adherence Clinic (MTAC), 12th Ed. [cited 2022 Oct 28] Available from: https://phisportal.moh.gov.my/sites/default/files/phis_attachments_39556/U.%20MANUAL_MTAC-12th%20E.pdf

[17] Pharmaceutical Services Programme, Ministry of Health Malaysia. Protocol Medication Therapy Adherence Clinic (MTAC) Psoriasis, 2nd Ed. 2021.

[18] Morisky Medication Adherence Research, LLC. (n.d,) MMAS License Pricing. [cited 2022 Oct 28] Available from: http://www.moriskyscale.com/mmas-license-pricing.html#/