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Quality of Life and Adherence to Imatinib Mesylate Therapy in Chronic Myeloid Leukemia Patients at Dharmais Cancer Hospital Jakarta

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ABSTRACT

Background: Quality of life and adherence to long-term imatinib mesylate (IM) therapy is a major factor in achieving therapeutic effects in patients with chronic myeloid leukemia (CML). However, the data of the quality of life and adherence level is inconsistent in various studies and is also not fully understood yet in Indonesia.

Methods: This is an observational study (single-centered) using a cross-sectional design. CML patients older than 18 years old with National Health Insurance (JKN) at the Dharmais Cancer Hospital (RSKD) Jakarta who used IM for at least one month were tested using the Medication Adherence Questionnaire (MAQ) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) from March to April 2020.

Results: A total of 50 CML patients were included in the study (male: female ratio = 1.08: 1), had a good median score of global health status/QoL, and had a good function and symptom scales, except for the fatigue symptom scale (median: 33.33; 25th percentile - 75th percentile: 11.11–44.44). The patient adherence rate was dominated by adherent patients (20/50; 40.0%). Comparative analysis revealed that the scale of QoL ($p = 0.028$) and fatigue ($p = 0.094$) variables showed statistically significant differences between adherent and non-adherent subjects.

Conclusions: This study showed that two-fifth of patients were considered to be non-adherent. Adherent patients were known to have higher QoL than non-adherent patients. Meanwhile, patients with severe symptoms of fatigue were found to be non-adherent to IM therapy.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm contributing to 15% of adult leukemia cases [1]. The annual mortality rate in the United States decreased from 10-20% to 2% after the introduction of tyrosine kinase inhibitors (TKIs) therapy [2]. The provision of TKIs therapy has changed the paradigm of malignancy from an untreatable disease entity into a chronic, controllable condition to increase life expectancy, as well as achieving treatment-free remission (TFR) [1,3]. Imatinib mesylate (IM) as one of the first generation TKIs was first approved as a monotherapy for patients with chronic phase CML [4].

Non-adherence is a significant challenge throughout the world, especially in chronic disease management in developed and developing countries [5]. Although cancer is a serious disease, non-adherence is also one of the difficulties faced by patients with cancer. In contrast to parenteral chemotherapy, which is given under the health care provider supervision, oral chemotherapy is highly dependent on the patient's commitment [6]. The systematic review of 14 articles regarding adherence to IM used in CML patients showed therapeutic adherence varies widely, ranging from 19 to 97% [7]. Adherence is a strong predictor of achieving an adequate molecular response in CML patients treated

with IM. Non-adherence to IM in CML patients can have serious consequences, which is associated with a lower rate of molecular response that can increase the progression of the disease [8,9]. Besides, non-adherence also had an impact on increasing the costs of treatment [10].

The quality of life (health-related quality of life/ HRQOL) outcome of CML patients with IM is known to be better than the previous standard therapy (the combination of interferon and cytarabine) [11]. However, in general, CML patients generally could not achieve a normal quality of life because of the decreased HRQOL associated with long-term CML therapy [12]. Due to the lack of information regarding the quality of life and level of adherence of patients using oral chemotherapy, especially IM in CML patients in Indonesia, the purpose of this study is to determine the quality of life and the level of adherence to IM use in CML patients at the Dharmais Cancer Hospital, Jakarta, Indonesia.

METHODS

This is an observational study (single-centered) using a cross-sectional design. The study was conducted at the Dharmais Cancer Hospital Jakarta from March to April 2020. This research had received ethical clearance by the Health Research Ethics Committee of the Dharmais Cancer Hospital Jakarta (No. 028/KEPK/ III/2019). All patients who consented to participate in the study signed a written informed consent form in accordance with the Helsinki Declaration.

The study respondents involved National Health Insurance patients with CML older than 18 years old and had been on IM therapy for at least one month. Consecutive sampling was used in patient selection. The exclusion criteria of this study comprised patients who could not be met at the hospital specifically at the Pharmacy Unit, were unwilling or did not sign the informed consent, and did not complete data requirements.

Primary and secondary patient data were collected. Primary data were based on patient self-reports using the study aid form, while secondary data were based on the medical records and the Dharmais Cancer Hospital Jakarta Information System. Data retrieval was done by the respondents who filled in the form directly or by a guided interview with a researcher. The research aid form was divided into three parts, namely information on basic characteristics, adherence, and quality of life.

Demographic, clinical, and therapeutic characteristics

Demographic, clinical, and therapeutic characteristics were obtained directly through a series of questions in the aid form, and some questions were confirmed using the Dharmais Cancer Hospital Jakarta Information System. Demographic characteristics data retrieved included age, gender, marital status, place of residence, and level of education. Meanwhile, the clinical and therapeutic characteristics data comprised the comorbidities, duration of IM therapy, and concurrent medications.

Measurement of adherence

Measurement of adherence was assessed using a self-reported method with the medication adherence questionnaire (MAQ) questionnaire. The MAQ questionnaire has been widely validated in various diseases and is used extensively in multiple studies [13]. The Indonesian Language version of the MAQ questionnaire has been tested for validation and reliability in previous studies [14]. The MAQ questionnaire consists of four questions related to the patient's difficulties to adhere to the assigned therapy with a score ranging from 0 to 4 [13]. Patients are considered adherent if they answer 'No' to all questions in MAQ (MAQ score = 0). Meanwhile, patients are considered non-adherent if they answer 'Yes' to any of the questions (MAQ score = 1–4) [15].

Quality of life measurement

The quality of life was assessed using the Indonesian version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) [16]. This measuring instrument consisted of 30 questions with one global health status (QoL) scale, five functional scales (physical, role, cognitive, emotional, and social), and three symptom scales (weakness, pain, and nausea/vomiting). Furthermore, the instrument also included other questions comprising dyspnea, loss of appetite, sleep disturbances, constipation, diarrhea, and financial impact on disease and therapy [17]. In general, the higher the QoL/function scale score is, the higher the quality of life/health function will be. However, in the symptom scale, the more severe/ disturbing the symptoms are, the higher the symptom scale score is obtained [18].

Statistical analysis

A descriptive analysis was carried out for each of the research variables. Categorical variables are presented in the form of a frequency distribution (percentage) for baseline characteristics (demographic, clinical, and therapeutic) and the level of adherence based on the MAQ. Meanwhile, the numerical data was obtained from the EORTC QLQ-C30 score using the median and interquartile ranges due to the data not normally distributed using the Shapiro-Wilk normality test. Furthermore, a comparative analysis between adherent and non-adherent patients with the quality-of-life dimensions was performed with the Mann-Whitney test. A two-tailed p-value < 0.05 was considered

statistically significant. All statistical analyzes were performed using the IBM SPSS (Statistical Package for Social Science) program version 22.0.

RESULTS

Demographic, clinical, and therapeutic characteristics

A total of 50 CML patients with IM were included in the study. The patients' mean age was 36.13 (33.03–39.24) years with a male: female ratio of 1.08:1. The majority of patients (76.0%) are married, lived in Jabodetabek (Jakarta and its surrounding cities) (92.0%), and have received higher education (52.0%). The research subjects were predominantly without any comorbid (90.0%). The mean duration of IM therapy was 3.99 (3.11–4.87) years without any other drug combination (76.0%). The distribution of the patients' characteristics can be seen in **Table 1.**

Measurement of adherence

The percentage of adherence level and the distribution results of the MAQ can be seen in **Figure 1** and **Figure 2**, respectively. As many as 30 patients (60.0%) adhered to the assigned IM treatment while 20 others (40.0%) did not. Patient non-adherence was dominated by unintentional non-adherence reasons (the first question of the MAQ questionnaire), namely that 34.0% of patients answered that they had forgotten to take medication. Meanwhile, there were no patients who answered that they did not care about IM treatment for the second question. However, it was found that only a small proportion of patients answered with other intentional non-adherence reasons, namely 2.0% for the third question and 6.0% for the fourth question of the MAQ. There was one patient who answered "Yes" for the first and fourth questions.

Quality of life measurement

Based on EORTC QLQ-C30 scoring, the median total score of the QoL was 83.3 (25th percentile – 75th percentile: 75.0–85.4). The function scale, physical, role, emotional, cognitive, and social functions, had a median total score of more than 85.0. Meanwhile, for the symptom scale, fatigue was an irritating symptom. Based on the comparative analysis of adherence with quality-of-life dimensions (**Table 2**), only the QoL (p = 0.028) and fatigue (p = 0.094) variables showed statistically significant differences between adherent and non-adherent subjects. The scores for each dimension of quality-of-life based on the EORTC QLQ-C30 questionnaire can be seen in **Table 2**.

Table 1. Demographic, clinical and therapeutic characteristics of patients

Variables	Category	n (%)
Age	≤ 40 years	24 (48.0)
	> 40 years	26 (52.0)
Gender	Male	26 (52.0)
	Female	24 (48.0)
Marital status	Single/divorced/widow	12 (24.0)
	Married	38 (76.0)
Place of residence	Outside Jabodetabek	4 (8.0)
	Jabodetabek	46 (92.0)
Education status	High school or less	24 (48.0)
	College graduation or more	26 (52.0)
Comorbidities	No	45 (90.0)
	Yes	5 (10.0)
Duration of IM	> 2 years	35 (70.0)
	≤ 2 years	15 (30.0)
Concomitant medications	No	38 (76.0)
	Yes	12 (24.0)

IM: imatinib mesylate; Jabodetabek: Jakarta and its surrounding cities

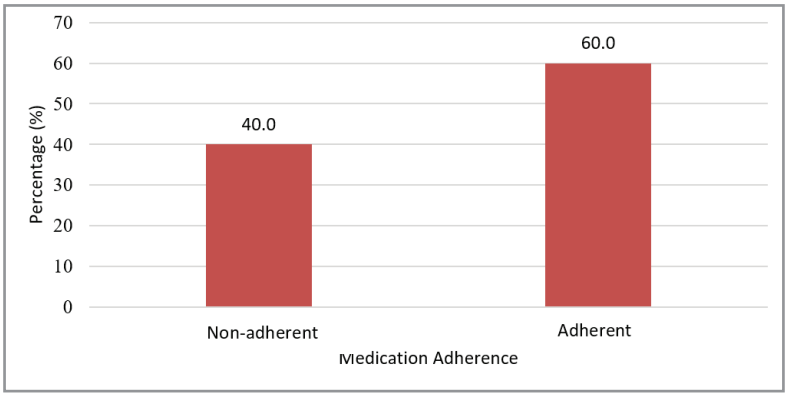

Figure 1.
Distribution of adherent and non-adherent based on MAQ (n = 50)

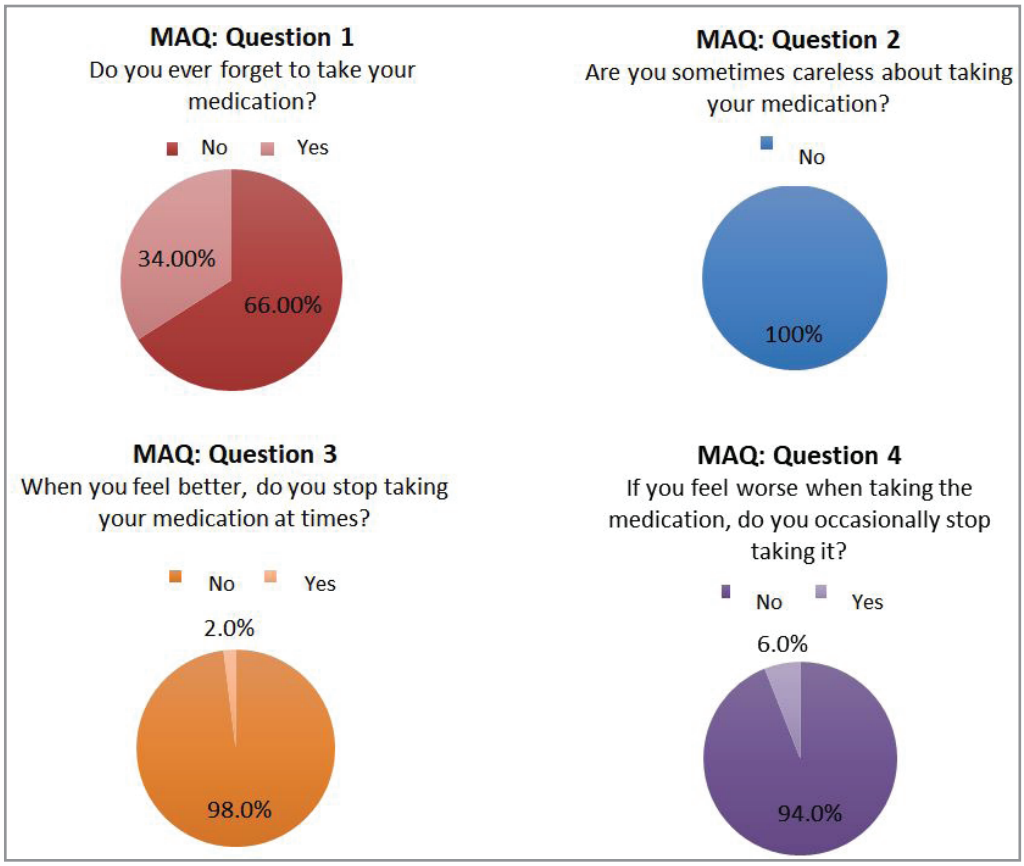

Figure 1.
Distribution of responses to each item on 4-item MAQ

Table 2.
Quality of life-based on EORTC QLQ-C30

EORTC QLQ-C30 Variables	Median Score (25th percentile–75th percentile)		p
	Non-adherent	Adherent	
Global Health Status/QoL	83.3 (68.7–83.3)	83.3 (81.2–91.7)	0.028
Functioning Scale			
Physical functioning	86.7 (80.0–100.0)	93.3 (86.7–100.0)	0.270
Role functioning	100.0 (83.3–100.0)	100.0 (83.3–100.0)	0.613
Emotional functioning	91.7 (75.0–100.0)	95.8 (83.3–100.0)	0.318
Cognitive functioning	91.7 (70.8–100.0)	100.0 (83.3–100.0)	0.787
Social functioning	100.0 (83.3–100.0)	100.0 (83.3–100.0)	0.735
Symptom Scale			
Fatigue	38.9 (22.0–44.4)	22.2 (0.0–44.4)	0.094
Nausea and vomiting	0.0 (0.0–29.2)	0.0 (0.0–16.7)	0.388
Pain	0.0 (0.0–33.3)	0.0 (0.0–16.7)	0.435
Dyspnoea	0.0 (0.0–00.0)	0.0 (0.0–00.0)	0.752
Insomnia	0.0 (0.0–33.3)	0.0 (0.0–33.3)	0.537
Appetite lose	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.710
Constipation	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.673
Diarrhea	0.0 (0.0–33.3)	0.0 (0.0–8.3)	0.376
Financial difficulties	0.0 (0.0–33.3)	0.0 (0.0–33.3)	0.357

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; QoL, quality of life

DISCUSSION

Achieving 100% treatment adherence in CML patients is a challenge. This is due to the long-term therapy that asymptomatic patients with chronic disease must undergo [19]. This study revealed that only 30 patients (60%) adhered to the CML treatment protocol using IM. Similar to studies in India and Belgium, IM therapy adherence in CML patients as measured using a similar subjective self-reported adherence measurement tool method was in the range of 45–67.3% [9,20]. Unnikrishnan et al. [20] revealed that patient non-adherence was dominated by unintentional non-adherence reasons reported in 33 to 44% of patients (based on the Morisky Medication Adherence Scale/MMAS-8 questionnaire). However, it differed in the reasons for intentional non-adherence; in that study, it was reported to be higher to a great extent than our study, which was at 43 to 52%.

The advancement in IM therapy or other TKI agents had improved the prognosis of CML patients. However, due to the long-term use of TKIs in patient CML therapy, it is important to obtain information related to the quality of life of patients in order to achieve comprehensive therapeutic effectiveness [21]. The global health status score of the subjects of this study is known to be higher when compared to the population of CML patients using IM in Turkey (mean: 57.2 ± 22.1) and Italy-Germany (mean: 67.47 ± 22.1), which were measured with a similar method, the EORTC-QLQC30 questionnaire [22,23].

The median score for all dimensions of the function scale in this study has obtained a score above 85.00. Compared to the acquisition of a functional scale score of Efficace et al. [22] and Uğur et al. [23], this study population shows superior functional scales, both the scales of function, role, emotion, cognitive, and social. Patients receiving IM are known to have better daily functional status and well-being, lower emotional or cognitive-related problems than patients who received the previous standard therapy [11].

One-third of patients with chronic phase CML with TKIs experience moderate symptoms that interfere with daily functional status [24]. The symptom scale score calculation showed chronic fatigue was the most irritating symptom for the subjects in this study. As many as 82% reported different degrees of chronic fatigue. It is known to be the most frequently reported symptom [25]. A further study conducted by Efficace et al. [22] revealed that chronic fatigue was a significant factor that depressed HRQOL in patients receiving IM. This fatigue did not appear as a singular symptom but correlated with musculoskeletal pain and muscle cramps. Multivariate analysis of the study population showed chronic fatigue was the only known variable that consistently affected the quality of life [26].

The comparative analysis of this study showed that the quality of life, as measured by the QoL score, was different between adherent and non-adherent subjects. This is reinforced by the final results of multivariate analysis in other IM studies, both in the CML patient population and the patient population with GIST, which revealed the QoL factor to be a strong predictor of adherence to IM therapy [20,27].

Symptom burden due to IM use became a major factor associated with poor adherence to TKIs and was associated with suboptimal therapeutic response and increased healthcare costs [28]. Therefore, it is important to evaluate Adverse Events (AEs) and tolerability to therapy in patients with CML. If AEs management is not carried out, decreased adherence occurs and results in discontinuation of therapy. Intervention measures by assisting patients in identifying and managing AEs can optimize patient adherence and lead to a better response to treatment therapy [8,21]. In addition to patient education and monitoring are known to increase adherence rates in CML patients with IM [29], the use of patient-reported outcomes (PRO) in assessing the effect of therapy on quality of life and AEs are also important as information in patient care and improving the quality of the health system. This is because the health care provider can get another perspective from the patient on the burden of disease and the effects of therapy [30].

This study has several limitations. The data collection was carried out at one point in time, and the number of subjects was limited, and sampling was only carried out at the Dharmais Cancer Hospital Jakarta (single-center study). The measurement of adherence is only based on the subjective method. Despite no gold standard regarding adherence measurement, a combination of measurement, such as subjective and objective methods, is recommended. Besides, the quality-of-life measurement only uses the EORTC-QLQC30 questionnaire, which is usually utilized for the general cancer population, not supported with a specific questionnaire for the CML population, i.e., EORTC QLQ-CML24. Another weakness of this study is that the evaluation was only limited to adherence and quality of life. In addition, the therapeutic outcome and factors affecting adherence were not assessed in this study. Comprehensive evaluations will provide a more complete understanding of the clinical outcomes and actual therapeutic effectiveness.

CONCLUSIONS

Two-fifth of CML patients with IM therapy were considered to be non-adherent. Fatigue is a disturbing symptom. Dimensions of QoL and fatigue showed statistically significant differences between adherent and

non-adherent subjects. Periodic assessment and intervention of quality-of-life dimension for each patient are imperative to be routinely exercised. Besides, educational and monitoring interventions related to disease and therapy, especially the management of AEs, can improve adherence and therapy outcomes of CML patients with IM.

DECLARATIONS

Competing of Interest

The authors declare no competing interest in this study.

Ethics Approval

This research had received ethical clearance by the Health Research Ethics Committee of the Dharmais Cancer Hospital Jakarta (No. 028/KEPK/III/2019). All patients who consented to participate in the study signed a written informed consent form in accordance with the Helsinki Declaration.

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