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Side effects and medication adherence of tyrosine kinase inhibitors for patients with chronic myeloid leukemia in Taiwan

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Abstract

Nonadherence is common in patients with chronic myeloid leukemia (CML) and leads to treatment failure and poor outcomes. Side effects due to treatment are also common in patients with CML. However, no study has investigated the link between side effects and medication adherence for patients with CML in Taiwan. Therefore, the aim of our study was to explore the influence of side effects on medication adherence in Taiwanese patients with CML.

CML in chronic-phase patients treated with breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1 tyrosine kinase inhibitors were recruited. We designed a questionnaire to collect baseline patient information, medication adherence (measured using the 8-item Morisky Medication Adherence Scale), and side effects. Clinical outcomes were assessed by the 3-month early molecular response rate and the 12-month major molecular response rate. Statistical comparisons of different parameters between adherent and nonadherent groups were conducted.

Fifty-eight patients were enrolled in this study, and 31% of them had poor adherence. The lack of information about treatment and medication was the major reason for poor medication adherence. Patients who were younger and unmarried were prone to poor adherence. The occurrence of side effects carried no statistically significant influence on adherence. Poor adherence resulted in a poor treatment response (lower 3-month early molecular response rate and lower 12-month major molecular response rate).

Poor adherence is common in Taiwanese patients with CML. The main reason for a decrease in the adherence rate is the lack of comprehensive information about treatment and medication, particularly in young and single population. The next urgent step is to educate patients about their treatment and management of side effects to improve adherence and treatment outcome for patients with CML in Taiwan.

Abbreviations: CI = confidence intervals, CML = chronic myeloid leukemia, EMR = early molecular response, GI = gastrointestinal, MMAS-8 = 8-item Morisky Medication Adherence Scale, MMR = major molecular response, OR = Odds ratio, SD = standard deviation, SI = international system, TKI = tyrosine kinase inhibitor.

Keywords: chronic myeloid leukemia, medication adherence, side effects, Taiwan, tyrosine kinase inhibitor

1. Introduction

Chronic myeloid leukemia (CML) is a hematopoietic stem-cell disease characterized by positive Philadelphia chromosome, a reciprocal translocation between chromosome 9 and 22 with the formation of a breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1 (*BCR-ABL1*) fusion oncogene. This oncogene induces deregulated myeloid cell growth and promotes uncontrolled proliferation.[1] Since the first BCR-ABL1 tyrosine kinase inhibitor (TKI), imatinib, was developed, CML prognosis has improved dramatically.[2] Newer TKIs became available for first-line treatment of chronic phase CML in 2010; these so-called second generation inhibitors include nilotinib and dasatinib. The development of BCR-ABL1 TKIs in CML treatment has turned the disease into a chronic but manageable illness. However, adhering to the BCR-ABL1 TKI regimen is an important issue for patients with CML. Several studies have shown that nonadherence to BCR-ABL1 TKIs is common and results in treatment failure and poor outcomes for patients with CML.[3–5] Factors affecting medication adherence among patients with CML include patient characteristics, disease and treatment characteristics, social characteristics, and health care characteristics.[6] Previous studies have shown that adherence by patients with CML was influenced by side effects due to CML TKIs.[3,7] A study conducted in Taiwanese patients with CML by Chen et al also found that side effects were the main reasons that patients altered their therapy.[8] However, no study has directly explored the link between side effects and medication adherence to CML TKIs in Taiwan. The aim of our study was to clarify the influence of side effects on adherence in Taiwanese patients with CML and the association between adherence and treatment outcomes using a designed questionnaire.

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2. Method

2.1. Study design and participant recruitment

This study was a retrospective cross-sectional study and was conducted from January 2015 to June 2015 at the oncology outpatient clinics in a medical center in Southern Taiwan. Ethical approval was obtained from the Institutional Review Board of Kaohsiung Medical University Hospital. Eligible patients included those who were diagnosed with CML in chronic phase and received BCR-ABL1 TKI (imatinib, dasatinib, and nilotinib) treatment for more than 3 months; regularly visited oncology outpatient clinics; were able to communicate using either Mandarin or Taiwanese; had no cognitive impairment; and had not received an allogeneic hematopoietic stem-cell transplant. Informed consent was obtained from all individual participants included in the study. After informed consent was obtained, patients were interviewed and instructed by a research assistant to fill in the questionnaire.

2.2. Questionnaire design

We designed a questionnaire to collect data for patient-reported side effects and medication adherence. The questionnaire consisted of 3 parts. The first part was designed to collect patients' baseline and social characteristics, including age, sex, educational level, marital status, concomitant drug burden, and comorbidities (measured using the Charlson comorbidity index).[9] The second part was a validated 8-item Morisky Medication Adherence Scale (MMAS-8, Chinese version) to evaluate patient adherence.[10–12] A MMAS-8 score of <6, 6 to 7, and 8 is regarded as low, medium, and high adherence, respectively.[10–12] A MMAS-8 score of <6 was defined as nonadherence in our study. The last part was designed to collect the profiles of common nonhematologic side effects, such as skin rash, gastrointestinal (GI) upset, edema, headache, myalgia, malaise, and pleural effusion when taking TKIs. In addition, we asked 2 questions to survey if the appearance of side effects and lack of information about treatment altered medication adherence.

2.3. Treatment response evaluation

We evaluated the molecular response of patients with CML using buffy coat from approximately 10 mL of peripheral blood every 3 months using quantitative real-time polymerase chain reaction to measure *BCR-ABL1* transcript levels, expressed as BCR-ABL1% on the SI (international system) units.[13] The 3-month early molecular response (EMR) rate and the 12-month major molecular response (MMR) rate were collected retrospectively from chart review as primary endpoints to evaluate the treatment response to TKIs in our study. EMR is defined as BCR-ABL1 <10% and MMR is defined as BCR-ABL1 <0.1%.[14]

2.4. Side effects evaluation

The evaluation of side effects was classified as nonhematologic side effects and hematologic side effects. Nonhematologic side effects were obtained from the questionnaire provided to participants, and included skin rash, GI upset, edema, headache, myalgia, malaise, and pleural effusion. The hematologic side effects, such as leukopenia, anemia, and thrombocytopenia, were collected by chart and data review.

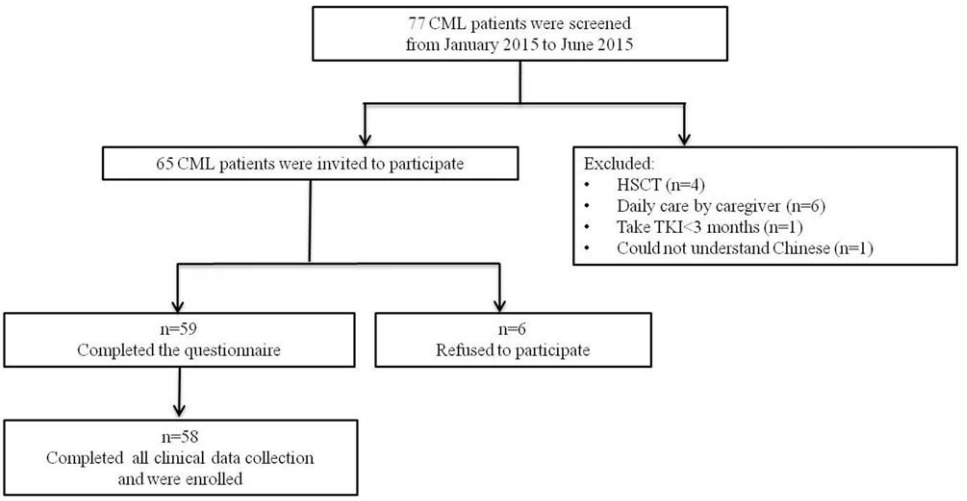
2.5. Statistical analysis

Statistical comparisons of baseline characteristics, side effects, and answers to the 2 questions about adherence and non-adherence were conducted. The Student *t* test or nonparametric statistics were utilized to test for statistically significant differences in continuous variables, while Chi-squared or Fisher exact tests were used for categorical variables. Logistic regression was also used to examine the predictors of the 3-month EMR rate and the 12-month MMR rate. Odds ratios (ORs) and their 95% confidence intervals (CIs) were presented for all covariates included in the logistic regression model. All tests were 2-sided and statistical significance was defined at $P < .05$.

3. Results

3.1. Baseline characteristics and medication adherence in patients with CML

A total of 58 out of 77 eligible patients who completed the survey were enrolled in this study (Fig. 1). Most patients were male (n = 39, 67.2%), married (n = 38, 65.5%), and had a high



CML: chronic myeloid leukemia, HSCT: hematopoietic stem cell transplant, TKI: tyrosine kinase inhibitor

Figure 1. Algorithm of patient recruitment.

Table 1

Baseline characteristics of patients with chronic myeloid leukemia.

Parameters	Total (n = 58)
Male, n (%)	39 (67.2)
Age at study entry (y)	
Median	50
Range	20–83
Marital status, n (%)	
Married	38 (65.5)
Education level,* n (%)	
Elementary school	8 (13.8)
Junior high	4 (6.9)
Senior high	20 (34.5)
University degree or higher	26 (44.8)
Charlson Comorbidity Index, n (%)	
0	23 (39.7)
1	10 (17.2)
2	7 (12.0)
≥3	18 (31.1)
Concomitant drug burden, n (%)	
0	36 (62.1)
1	5 (8.6)
2–5	15 (25.9)
≥6	2 (3.4)
Current TKI therapy, n (%)	
Imatinib	22 (47.9)
Dasatinib	26 (44.8)
Nilotinib	10 (17.3)
Duration of TKIs treatment (y)	
Mean (SD)	5.27 (3.56)
Range	0.4–12.9
Nonhematologic side effect experience, n (%)	
Yes	51 (87.9)
Hematologic side effect, n (%)	
Leukopenia	23 (39.7)
Anemia	12 (20.7)
Thrombocytopenia	36 (62.1)

SD = standard deviation, TKI = tyrosine kinase inhibitor.

* Educational levels equal to or higher than senior high school were regarded as high educational levels and others were regarded as low educational levels.

Table 2

Baseline characteristics between adherent and nonadherent groups.

	Medication adherence		
Variables	Adherence	Nonadherence	*P*-value
Sex (male), n (%)	26 (65.0)	13 (72.2)	.59
Age, mean (SD), y	51.9 (15.4)	42.3 (12.2)	.02*
Education level,† n (%)			.74
High	31 (77.5)	15 (83.3)	
Low	9 (22.5)	3 (16.7)	
Marital status, n (%)			.02*
Married	30 (75.0)	8 (44.4)	
Unmarried	10 (25.0)	10 (55.6)	
Charlson comorbidity index, n (%)			.62
0	15 (37.5)	8 (44.4)	
≥1	25 (62.5)	10 (55.6)	
Concomitant drug, n (%)			.29
No	23 (57.5)	13 (72.2)	
Yes	17 (42.5)	5 (27.8)	
Duration of TKI treatment, mean (SD), y	5.03 (3.73)	5.81 (3.21)	.45
TKI type, n (%)			.29
Imatinib	17 (42.5)	5 (27.8)	
Dasatinib, nilotinib	23 (57.5)	13 (72.2)	

SD = standard deviation, TKI = tyrosine kinase inhibitor.

* $P < .05$.

† Educational levels equal to or higher than senior high school were regarded as high educational levels and others were regarded as low educational levels.

educational level (n = 46, 79.3%). The median age was 50 years (range: 20–83 years). Among them, 23 patients (39.7%) had a Charlson comorbidity index of 0 points and 17 patients (29.3%) received at least 2 other concurrent drugs for comorbidities. The mean duration of TKI treatment was 5.27 years (standard deviation, 3.56 years). At the time of interview, 22 patients (47.9%) were receiving imatinib, 26 patients (44.8%) were receiving dasatinib, and only 10 (17.3%) patients were receiving nilotinib. Among the 26 patients who were receiving dasatinib, 14 patients used as the medication as first line treatment, 11 patients had dasatinib as second line treatment and shifted from imatinib due to suboptimal response or treatment failure, and 1 patient was shifted from nilotinib due to difficultly controlling hyperglycemia. Among the 10 patients who were receiving nilotinb, this was first line treatment for 2 patients, second line treatment for 7 patients who were shifted from imatinib due to suboptimal response or treatment failure, and 1 patient was shifted from dasatinib due to pleural effusion (Table 1).

The median adherence score measured by MMAS-8 was 6 (range 1–8), indicating medium adherence. The results of the study revealed that 17 (31.0%) patients showed high adherence, 23 (37.9%) showed medium adherence, and 18 (31.0%) showed low adherence; the latter was defined as nonadherence based on our definition.

3.2. Association between baseline characteristics and medication adherence

From our study, older age ($P = .02$) and married status ($P = .02$) were found to be associated with better adherence. Other characteristics, such as sex, educational level, comorbidities, concomitant drug number, duration of TKI treatment, and TKI type showed no difference between adherent and nonadherent patients (Table 2).

3.3. Link between side effects and medication adherence

Most patients (87.9%) were reported to have at least 1 nonhematologic side effect. The hematologic side effects of TKIs were common, and 39.7% of patients had leukopenia, 20.7% had anemia, and 62.1% had thrombocytopenia (Table 1). The frequency of patient-reported nonhematologic side effects and hematologic side effects was not found to be statistically related to patients' adherence. Regarding the question "Have you ever reduced or stopped your drugs because of their side effects?," 37.8% of patients had ever reduced or stopped their TKI due to side effects, but only 2 patients (3.4%) discontinued and shifted to other TKIs due to side effects from our chart record. Our results showed that there was no statistically significant correlation between the occurrence of side effects and medication adherence. However, the lack of information about treatment and medication considerably reduced patients' adherence to TKIs (Table 3).

Table 3

Association between side effects and medication adherence.

Side effects	Medication adherence		
	Adherence	Nonadherence	*P*-value
Skin rash, n (%)			.54
Yes	13 (32.5)	4 (22.2)	
No	27 (67.5)	14 (77.8)	
Edema, n (%)			.34
Yes	13 (32.5)	7 (38.9)	
No	27 (67.5)	11 (61.1)	
Headache, n (%)			.54
Yes	30 (75.0)	4 (22.2)	
No	10 (25.0)	14 (77.8)	
Myalgia, n (%)			.24
Yes	20 (50.0)	6 (33.3)	
No	20 (50.0)	12 (66.7)	
GI upset, n (%)			.83
Yes	21 (52.5)	10 (55.6)	
No	19 (47.5)	8 (44.)	
Fatigue, n (%)			.86
Yes	21 (52.5)	9 (50.0)	
No	19 (47.5)	9 (50.0)	
Pleural effusion, n (%)			1.00
Yes	3 (7.5)	1 (5.6)	
No	37 (92.5)	17 (94.4)	
Leukopenia, n (%)			.22
Yes	18 (45.0)	5 (27.8)	
No	22 (55.0)	13 (72.2)	
Anemia, n (%)			.74
Yes	9 (22.5)	3 (16.7)	
No	31 (77.5)	15 (83.3)	
Thrombocytopenia, n (%)			.20
Yes	27 (67.5)	9 (50.0)	
No	13 (32.5)	9 (50.0)	
Two designed questions	**Adherence**	**Nonadherence**	***P*-value**
Have you ever reduced or stopped your drugs because of their side effects? n (%)			.12
Yes	4 (10.0)	5 (27.8)	
No	36 (90.0)	13 (72.2)	
Will you decrease your medication adherence because there is no comprehensive information about treatment and medication? n (%)			.03*
Yes	2 (5.0)	5 (27.8)	
No	38 (95.0)	13 (72.2)	

* $P < .05$.

3.4. Relationship between medication adherence and treatment outcome

The 3-month EMR rate was found to be higher in patients who were married (OR 0.16, 95% CI 0.03–0.79; $P = .03$) and in those with higher adherence scores (OR 2.85, 95% CI 1.45–5.61; $P = .002$) based on univariate analyses. However, it was only significantly associated with patient adherence (OR 2.69, 95% CI 1.35–5.35; $P = .005$) when further multivariate analyses were performed (Table 4). Multivariate analyses showed that the type of TKI (reference, first-generation TKI, imatinib, OR 7.67, 95% CI 1.62–36.4; $P = .01$) and patient adherence to TKIs (OR 1.73, 95% CI 1.13–2.65; $P = .01$) were the only 2 factors significantly associated with the 12-month MMR. Patients who received second-generation TKIs, nilotinib and dasatinib, and maintained good adherence showed an improved 12-month MMR rate (Table 5).

4. Discussion

The objectives of our study were to investigate the medication adherence for patients with CML in Taiwan and to clarify the influence of side effects on adherence in Taiwanese patients with CML. According to the study results, 31% of patients were regarded as nonadherent. When considering the association between baseline characteristics and medication adherence, older age, and married status showed a trend toward better adherence. However, there is conflicting evidence in the literature as to whether age influences adherence in patients with CML. While there are some reports showing that adherence is higher in elderly patients,[3,15] other studies suggest that adherence is lower in elderly patients[16] or that age has no significant impact on adherence.[5,17] In addition, marital status was also found to be associated with adherence, with married status associated with a better adherence to TKIs in our patients with CML. A meta-analysis of the general medical literature concluded that adherence to medical recommendations was higher in married patients.[18] This increased adherence may be the result of practical family support (eg, reminding the patient to take medications).

From our study, dasatinib was the most commonly (26 out of 58 patients) used TKI. Dasatinib was used as first line treatment by 14 patients, and 12 patients were shifted from imatinib to dasatinib as second line treatment. The reason why dasatinib is more frequently used than other TKIs may be contributed to 2 points. First, the DASISION and ENESTnd trials showed that second generation TKIs, dasatinib and nilotinib, had a faster and deeper molecular response than imatinib.[19,20] Therefore, most

Table 4

Logistic regression analyses of 3-month early molecular response rate.

Variables	3-month EMR rate		3-month EMR rate (adjusted)*	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex (reference male)	2.00 (0.36–11.21)	.43		
Age	1.03 (0.98–1.08)	.28		
Charlson comorbidity index	1.41 (0.89–2.23)	.15		
Education level (reference low)	1.29 (0.21–7.80)	.79		
Marital status (reference married)	0.16 (0.03–0.79)	.03†	0.39 (0.05–2.92)	.36
Type of TKI (reference imatinib)	0.17 (0.02–1.52)	.11		
Adherence score	2.85 (1.45–5.61)	.002†	2.69 (1.35–5.35)	.005†

CI = confidence interval, EMR = early molecular response, MMR = major molecular response, OR = odds ratio.

* Adjusting variables for multivariate analysis: marital status and adherence score.

† $P < .05$.

Table 5

Logistic regression analyses of 12-month major molecular response rate.

Variables	12-month MMR rate		12-month MMR rate (adjusted)*	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex (reference male)	2.08 (0.50–8.71)	.32		
Age	1.04 (0.99–1.08)	.11		
Charlson comorbidity index	1.23 (0.87–1.72)	.24		
Education level (reference low)	1.36 (0.34–5.45)	.66		
Marital status (reference married)	0.41 (0.12–1.42)	.16		
Type of TKI (reference imatinib)	3.68 (1.06–12.8)	.04†	7.67 (1.62–36.4)	.01†
Adherence score	1.41 (0.99–2.00)	.05	1.73 (1.13–2.65)	.01†

CI = confidence interval, MMR = major molecular response, OR = odds ratio, TKI = tyrosine kinase inhibitor.

* Adjusting variables for multivariate analysis: type of TKI, and adherence score.

† $P < .05$.

clinicians in our hospital prefer to use second generation TKIs to treat newly diagnosed patients with CML. Second, the administration of dasatinib is more convenient than other TKIs. Dasatinib can be taken with or without a meal and is taken only once daily. As the median age of our patients was 50 years old, most patients worked during the daytime, and if given a choice, they favored the most convenient drug. However, different TKIs did not influence patient adherence in our study.

In regard to the association between side effects and adherence to TKIs, it has been reported that the physicians' perceptions of patient adherence and side effects of TKIs were largely different from patient-directed reports. The physicians' estimates of patient adherence were too optimistic and often underestimated the severity of side effects.[21,22] Therefore, we designed the questionnaire to survey the common side effects of TKIs, such as skin rash, GI upset, edema, headache, myalgia, malaise, and pleural effusion. We aimed to record the side effects directly from the patients' reports and to study the link between the occurrence of side effects and patients' adherence. In a previous study of patient-reported adverse drug reactions and their influence on adherence in patients with CML, it was reported that a very high proportion (97%) of patients suffered from at least 1 adverse drug reaction, and this was irrespective of patients' adherence.[23] Our result was similar to the previous study. From our study, most patients (87.9%) had at least 1 nonhematologic side effect. The nonhematologic and hematologic side effects were also unrelated to patients' adherence. Although some patients had ever reduced or stopped TKIs due to side effects, the discontinuation rate was not high, and only 2 patients (3.4%) shifted to other TKIs. Dose adjustment and suspension of medication improved side effects the majority of the time. Therefore, few patients discontinued their TKI due to side effects. Instead, a lack of information about treatment and medication was the main reason that patients altered their adherence. Therefore, to increase adherence in patients with CML, the first priority should be to provide patients with comprehensive information about their treatment and how to manage the side effects of TKIs.

There is a lot of evidence supporting the clinical benefits of patient adherence to TKIs.[3–5,16] In our study, we found that both the 3-month EMR and 12-month MMR rates were significantly better in adherent patients. In addition, patients receiving dasatinib and nilotinib achieved a better 12-month MMR rate. This result was consistent with the DASISION and ENESTnd trials showing that dasatinib and nilotinib had better efficacy with a faster and deeper molecular response than imatinib.[19,20]

There are some limitations to our study. First, not all factors influencing medication adherence were investigated. There were some other confounders, such as economic status of patients, physician characteristics, and health care systems, which were not included in our study. Because TKIs for patients with CML in Taiwan are completely covered by our National Health Insurance and the cost of molecular monitoring was also not paid by patients, financial hardship has fewer effects on medication adherence than in other countries, and was therefore not included in our analyses. Second, the study design was a retrospective cross-sectional study. The adherence and side effects were assessed by only one interview, and the treatment response was collected retrospectively from chart review. It would be difficult to infer the temporal association between adherence, side effects, and treatment response. Therefore, only an association, and not causation, can be inferred from this study. Third, number of patients included in our study was small. However, the study included several factors, such as sociodemographic backgrounds, disease, treatment characteristics, and particularly the patient-reported side effects for adherence analysis.

5. Conclusion

Poor adherence to TKI treatment was noted in 31% of patients with CML in Taiwan, especially in younger and unmarried patients. Poor medication adherence may lead to worse 3-month EMR and 12-month MMR rates. The lack of information about treatment and medication was the main concern that caused patients with CML to alter their adherence. The results from our study can help clinicians develop efficient strategies to improve adherence of patients with CML in Taiwan. The next steps are to implement educational programs with a particular focus on treatment and medication side effects to improve medication adherence in patients with CML in Taiwan.

Author contributions

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