

Evaluation of Imatinib Adherence in Chronic Myeloid Leukemia Patients in Babylon Province, Iraq

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Abstract

Background: Chronic myeloid leukemia is a clonal myeloproliferative neoplasm that results in proliferation, mainly of granulocytic components. Resulting from t(9;22) with fusion oncogen BCR-ABL1 which has uninhibited tyrosine kinase activity. The introduction of tyrosine kinase inhibitors, such as Imatinib, has significantly altered the management and prognosis of this condition, but poor adherence is still a significant factor in therapy failure. **Objective:** To measure chronic myeloid leukemia (CML) patients' adherence to Imatinib treatment and to analyze potential reasons for poor adherence. **Materials and Methods:** The study included 52 CML patients in the chronic phase treated with Imatinib for at least 12 months; 30 of them were women and 22 were men, with a median age of 45 years. Patient adherence to Imatinib was assessed using the Morisky Medication adherence scale. Response to treatment was assessed by the evaluation of the level of BCR-ABL1 mutation in peripheral blood. **Results:** Out of 52 patients, 17 were adherent to Imatinib while 35 of them were nonadherent. The patient's adherence status to Imatinib was found to have a significant effect on the response to treatment. The most common cause of nonadherence was forgetfulness. Age, sex, occupation, educational level, marital status, residence, duration of treatment, relation to meal time, taking other medications, and drug side effects have no significant effect on adherence. **Conclusions:** Adherence to Imatinib was poor and this has a negative impact on patients' response to therapy. Patients' forgetfulness was the most frequent reason for nonadherence, followed by drug-related patient disturbance.

Keywords: Adherence, CML, Imatinib

INTRODUCTION

Chronic clonal neoplastic proliferation of stem cells from all hematopoietic cell lines constitutes chronic myeloid leukemia (CML), which is most prevalent in the granulocytic component. Philadelphia (Ph) chromosome was created by the long limbs of chromosomes 9 and 22 being rearranged, along with a fusion oncogene. (BCR-ABL1). Tyrosine kinase inhibitor (TKI) treatment can be effectively cure Ph*/BCR-ABL1-positive CML.^[1] This mutation results in multi domain constitutively active chimeric tyrosine kinase conferring proliferative and antiapoptotic effects.^[2] The disease presents mainly at ages of 30–80 years, with a peak incidence at age of 55 years.^[1] The incidence of CML is 1–2 cases per 100,000 people worldwide per year, with a small male predominance.^[3] The incidence in Iraq is 2.079 per 100,000.^[4] TKIs have completely altered the conventional approach to treating

CML, which has a significant impact on the prognosis.^[3] Imatinib, Nilotinib, or Dasatinib are typically the first-line medications used to treat CML patients who are in the chronic phase. After Imatinib fails, other medications such as Nilotinib and Dasatinib may be used. In patients with the T315I mutation in the ABL1 gene, ponatinib has a distinctive effect. Asciminib has a distinct manner of adherence to ABL kinase, so it can be useful either in combination with other TKI or in the event of resistance results from ABL kinase mutation.^[5] Imatinib side effects include gastrointestinal upset, myalgias, and fatigue

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which are generally mild. Pruritis and fluid buildup around the eyes, feet, or abdomen may also be side effects. Cardiotoxicities, secondary cancer, myositis, MS, renal failure, dermatitis pancreatitis, hypophosphatemia, gynecomastia, hypogammaglobulinemia, opportunistic infections, hepatotoxicities, pulmonary toxicities, skin hyper/hypopigmentation, and cerebral edema are among the long-term side effects.^[6] An important contributor to treatment failure is poor adherence to TKIs treatment. According to the World Health Organization (WHO), adherence is the extent to which a person's behavior conforms to a medical staff's consensus recommendation.^[7,8] Patient education and continuous observation of their adherence are crucial in the achievement of optimal responses.^[9] In case of failure to achieve response milestones, assessment of adherence is required.^[3] In this article we assessed the adherence to Imatinib therapy of CML patients in Babylon Province in Iraq and trying to identify the factors leading to poor adherence.

MATERIALS AND METHODS

This cross-sectional study was conducted in Merjan Medical City, adult clinical haematology outpatient in Babylon Province in Iraq from June 2022 to December 2022.

Patient adherence to Imatinib was assessed using the Morisky Medication adherence scale (MMAS),^[10] as shown in Table 1. Arabic language was used to communicate with the patients.

Questions were taken by direct interview with patients in the outpatient clinic. Questions (1–8) were answered by (yes) or (no), in questions 1–4, 7 and 8, the answer (yes) given 0 point while answer (no) given 1 point, in questions 5 and 6 the answer (yes) given 1 point and (no) given 0 point. Question 9 was answered by (never) given 5 points, (once a while) 4 points, (sometimes) 3 points, (usually) 2 points and (all the time) 1 point.

The score ranged from 1 to 13 with patients achieved score 11 or above were considered adherent to Imatinib.

As a part of the routine follow-up for all CML patients visiting Merjan Medical City, the amount of BCR-ABL1 mutation in peripheral blood was evaluated to determine the treatment's effectiveness. Level of less than 0.1% was considered responding to treatment (major molecular response criteria according to ELN guidelines).^[11] Polymerase chain reaction method was used by calculating the fusion transcript copies relative to housekeeping gene copies to conclude the normalized copy number which can be monitored subsequently. The lower limit of detection by the assay was 0.0030.

Data were analyzed using Social Sciences of Statistical Package version 20.0 (IBM, Armonk, NY, USA), Chi square procedure was used to identify significant differences at the level of less than or equal to 0.05.

Ethical approval

The research ethics committee at the University of Babylon, College of Medicine of Hammurabi has reviewed and discussed the research study and approved it to be conducted in the presented form according to the document number 600 at 15/2/2023.

RESULTS

In all, 52 patients participated in the research. With a median age of 45 years, all of them had been identified with chronic phase CML and had been taking Imatinib for at least a year.

Seventeen patients were adherent to TKIs, whereas 35 of them were nonadherent according to MMAS. Ten of those who were adherent had optimal molecular response and 7 hadn't, while 17 of those who were nonadherent had optimal molecular response and 18 had not have. Effect of patients adherence status to Imatinib on their response was found to have significant effect on response to

Table 1: Morisky medication adherence scale

1. Do you sometimes forget to take your medication?	Yes	No
2. People may neglect to take their medicines for reasons other than simple forgetfulness. Consider the past two weeks. Were there any days when you neglected to take your medication?	Yes	No
3. Have you ever stopped taking your medicine without telling your doctor because it made you feel worse?	Yes	No
4. Do you ever forget to take your medication when you move or leave the house?	Yes	No
5. Did you take your prescription medicine yesterday?	Yes	No
6. Do you follow a specific schedule or get reminders to take your medication?	Yes	No
7. Do you ever decide to cease taking your medication because you believe your condition is under control?	Yes	No
8. Do you worry about taking your medication as prescribed? For some individuals, taking medications daily is a real hassle.	Yes	No
9. How frequently do you struggle to recall to take your medications?	Never Once a while Sometimes Usually All the time	

treatment, as shown in Table 2. The top three reasons for nonadherence were forgetfulness (affecting 24 patients), feeling harassed (15), feeling worse (affecting 11 patients), and not being available (2 patients due to pregnancy) and side effects (3 patients), as shown in Table 3.

Table 2: Patients adherence to Imatinib and their response

Class of adherence	Response		P value
	Optimal	Non optimal	
Adherent	10 (19.2%)	7 (13.4%)	0.039814
Nonadherent	17 (32.69%)	18 (34.61%)	
Total	52		

Table 3: Causes of nonadherence to Imatinib

Cause of nonadherent	Number
Forgetfulness	24 (46.1%)
Feeling hassled	15 (28.8%)
Feeling worse with drug	11 (21.1%)
Feeling disease under control	10 (19.2%)
Unavailability	2 (3.8%)
Pregnancy	2 (3.8%)
Side effect	3 (5.7%)

It was found that different parameters namely, sex, occupation, educational level, marital status, residence, having a way to remember to take the medication, duration of treatment, relation to meal time and taking other medications have no significant effect on adherence, as shown in Table 4.

Age distribution among the study participants is shown in Table 5, and the age has no significant effect on adherence.

Side effects were also reported with GI side effect being the most common. In general, the side effects have no significant effect on adherence, as shown in Table 6.

DISCUSSION

High percentage of patients treated with Imatinib were poorly adherent with their treatment, 67% of them were found to be nonadherent and only 33% were adherent. Poor compliance to Imatinib therapy has a negative effect on CML patient response.

The most common cause of nonadherence is forgetfulness followed by feeling annoyed from medication use, while the side effects occupy the last rank. The most common side effect was GI upset.

Table 4: Effect of different parameters on patients adherence to Imatinib

Variable		Total number	Class of adherence		P value
			Adherent	Nonadherent	
Sex	Female	30 (57.6%)	9 (17.3%)	21 (40.3%)	0.115
	Male	22 (42.3%)	8 (15.3%)	14 (26.9%)	
Occupation	Employed	18 (34.6%)	7 (13.4%)	11 (21.1%)	0.197
	Non employed	34 (65.3%)	11(21.1%)	23 (44.2%)	
Education level	Not educated	8 (15.3%)	1 (1.9%)	7 (13.4%)	0.128
	Primary	20 (38.4%)	6 (11.5%)	14 (26.9%)	
	Secondary	19 (36.5%)	9 (17.3%)	10 (19.2%)	
	College	4 (7.6%)	1 (1.9%)	3 (5.7%)	
Marital status	After college	1 (1.9%)	0 (0%)	1 (1.9%)	0.267
	Married	40 (76.9%)	14 (26.9%)	26 (50%)	
	Not married	9 (17.3%)	3 (5.7%)	6 (11.5%)	
	Divorced	1 (1.9%)	0 (0%)	1 (1.9%)	
Residence	Widowed	2 (3.8%)	0 (0%)	2 (3.8%)	0.99
	Rural	21 (40.3%)	7 (13.4%)	14 (26.9%)	
	Urban	31(59.6%)	10 (19.2%)	21 (40.3%)	
Duration of treatment	>3 years	5 (9.6%)	2 (3.8%)	3 (5.7 %)	0.23
	3–8 years	36 (69.2%)	12 (23%)	24 (46.1%)	
	<8 years	11 (21.1%)	3 (5.7%)	8 (15.3%)	
Relation to meal time	With	28 (53.8%)	7 (13.4%)	21 (40.3%)	0.14
	Before	8 (15.3%)	2 (3.8%)	6 (11.5%)	
	After	16 (30.7%)	7 (13.4%)	9 (17.3%)	
Taking other medications	Yes	13 (25%)	6 (11.5%)	7 (13.4%)	0.272
	No	39 (75%)	11 (21.1%)	28 (53.8%)	
Have a way to remember	Yes	32 (61.5%)	7 (13.4%)	25 (48%)	0.192
	No	20 (38.4%)	9 (17.3%)	11 (21.1%)	
Side effect	Yes	43 (82.6%)	14 (26.9%)	29 (55.7%)	0.115
	No	10 (19.2%)	5 (9.6%)	5 (9.6%)	

Table 5: Age distribution among study participant

Age group	Total	Adherent	Nonadherent	P value
<20	6 (11.5%)	3 (5.7%)	3 (5.7%)	0.086
20–39	13 (25%)	1 (1.9%)	12 (23%)	
40–59	22 (42.3%)	9 (17.3%)	13 (25%)	
60 and more	11 (21.1%)	4 (7.6%)	7 (13.4%)	

Table 6: Side effects of Imatinib

Side effect	No.	Adherent	Nonadherent
GIT upset	18 (34.6%)	7 (13.4%)	11 (21.1%)
Fatigue	5 (9.6%)	2 (3.8%)	3 (5.7%)
Neurological	6 (11.5%)	2 (3.8%)	4 (7.6%)
Sexual problem	1 (1.9%)	0 (0%)	1 (1.9%)
Musculoskeletal	5 (9.6%)	1 (1.9%)	4 (7.6%)
Skin	1 (1.9%)	0 (0%)	1 (1.9%)
Edema	6 (11.5%)	2 (3.8%)	4 (7.6%)
Fever	0 (0%)	0 (0%)	0 (0%)
Weight loss	1 (1.9%)	0 (0%)	1 (1.9%)

The effect of different parameters on patients adherence including age, gender, marital status, level of education, employment status, residence (living in a rural or urban area), side effects, other medications use, having way to remember, relation to meal time and duration of treatment were assessed without a significant effect on patients adherence.

According to a survey conducted at the Al-Hussain Cancer Center in the province of Karbala, 26.87% of their patients took Imatinib regularly. The most frequent reason for nonadherence was Imatinib supply, with forgetfulness coming in second. Third on the list of causes were side effects, with GI discomfort being the most frequent. Different parameters effect on adherence like gender, educational level, marital status and side effects were found to be nonsignificant.^[9]

A similar study was done in Qatar revealing that 61% of the patients were adherent to Imatinib and 39% were nonadherent, 65% due to financial causes and 13% due to drug unavailability. Different parameters effect on adherence including gender, educational level, marital status, lack of fund and side effect were found to be nonsignificant. The most common side effect was GI upset.^[12]

Another study was conducted in India reporting that a 25% of the patients were nonadherent to Imatinib and 75% were adherent, with depression and concomitant drug use were the most significant cause of nonadherence. Dyspepsia was the most common side effect. Different parameters effect on adherence including sex, educational level, employment status, and side effect, were found to be nonsignificant. While concomitant drug use was found to have a significant effect.^[13]

In Ethiopia, the study shown 55.1% adherence rate, with being rural with low income and the side effects were the most common parameters associated with nonadherence.^[14]

47% of the individuals in Brazil were nonadherent. The most frequent reasons for nonadherence to Imatinib were medication availability issues, and the most frequent side effects were GI distress and hematological disturbance. No significant effect was found between patient adherence and age and sex.^[15]

In Amsterdam, the study revealed non adherence in 25% of the study group with forgetfulness being responsible for 25% of the causes followed by feeling disturbed by drug use and avoidance of side effects.^[16]

In Saudi Arabia, a study of TKI adherence was conducted using the pill count method in King Abdulaziz Medical city with 56% of patients were found to be adherent to Imatinib and the main reasons for nonadherence were drug toxicity followed by forgetfulness. Different parameters were found to have a significant effect on patient adherence including age, level of education and duration of the disease while poly pharmacy was not.^[17]

In general, the results of this article were consistent with that of above studies with some differences, which can be explained by differences in sample size and countries character.

CONCLUSION

This is the second study for Imatinib adherence in Iraq and the first one in Babylon province. Unfortunately, adherence to Imatinib in Babylon was poor and it was found to have a negative impact on patient response to therapy. The most frequent reason for nonadherence was patient forgetfulness, followed by patient disturbance from drug use. The healthcare practitioners should address these issues by carefully crafting an educational program and conducting more frequent follow-ups.

Further studies with a larger number of patients, drugs, and centers, with a greater focus on the possible factors that may affect the adherence is advised.

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Conflicts of interest

There are no conflicts of interest.

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