

Imatinib Mesylate Adherence in Chronic Myeloid Leukemia Patients: Data from Middle Euphrates Region of Iraq

Ahmed Mjali^{a*}, Saja Khudhiar Abbas^b

^{1,2}Department of Hematology /Oncology, Al- Hussein Medical City, Karbala, Iraq.

*Correspondence should be addressed to: ahmedmajly@yahoo.com

Abstract

Background: Chronic myeloid leukemia (CML) represents about one quarter of leukemia cases in our region making it a great challenge to the health system.

Aims: Since adherence to imatinib contributes to optimal cytogenetic and molecular responses in CML patients, our study tries to evaluate imatinib adherence in Middle Euphrates region of Iraq.

Materials & Methods: This study was conducted in Al-Hussein cancer center in Karbala province of Iraq between November 2011 and August 2019. There were 67 CML patients treated with imatinib, their adherence was assessed by using the 9-items Morisky Medication Adherence Scale, while response was evaluated by measuring *BCR-ABL1* transcription level in peripheral blood.

Results: Only 26.87% of our patients were adherent. Unavailability of drug was the most common cause of poor adherence in 73.13% of patients. Patients with good adherence were more likely to achieve an optimum response (P value =0.007).

Conclusion: Our results showed that adherence to imatinib was very low in our region. Economic factor (Unaffordable drug prices) was the main cause leading to suboptimal response. Therefore, efforts should be made to provide drugs to our patients. That will help in improve adherence and treatment outcomes.

Keywords: Imatinib, Adherence, Chronic Myeloid Leukemia, Iraq.

Introduction

Chronic myeloid leukemia (CML) is a condition of myeloproliferative disease caused by a constitutively active BCR-ABL tyrosine kinase generated by Philadelphia (ph) chromosome translocation.^{1,2} In 2017 an estimated more than 8 000 people diagnosed with CML in US, more than 1,000 people died from this disease.³ CML treatment has now been revolutionized by the introduction of tyrosine kinase inhibitors (Imatinib) leading to a substantial improvement in prognosis, response rate, overall survival and patients outcomes compared with previous therapeutic regimens.^{4,5}

Medical non-compliance has been described as a significant public health issue that lead to a significant financial burden on current healthcare systems. The World Health Organization (WHO) describes compliance as the extent to which a patients' behavior taking medication corresponds with agreed recommendations from a health-care provider.⁶

In US poor adherence to treatment has been estimated to cost \$100 billion each year, that represents 10% from hospital admissions and 23% from nursing homes admissions. In the same time lack of compliance to medical advice is also a source of ongoing frustration to health care workers.⁷

In this study we try to assess adherence of CML patients to imatinib in Middle Euphrates region of Iraq. This study can

help to analyze the factors that lead to poor compliance and

Table 1. The 9-item MMAS to calculating and evaluate imatinib adherence.

1. Do you sometimes forget to take your medication?	Yes/No
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?	Yes/No
3. Have you ever cut back or stop taking your medication without telling your doctor, because you felt worse when you	Yes/No

to develop future leukemia treatment strategies in our war-torn country.

Materials and Methods

This study was conducted in Al - Hussein cancer center in Karbala province of Iraq. This center was established in November 2011 with oncology & hematology wards. It covers not only Karbala population but also other patients from the Middle Euphrates region in Iraq are referred to this center for treatment of solid & hematological malignancy.⁸

A total of 67 Philadelphia positive CML patients treated with imatinib for at least 12 months, during period between November 2011 and August 2019 were included in our study. Patients adherence was evaluated by using the nine items Morisky Medication Adherence Scale (9-MMAS), which is one of the most commonly used technique for adherence assessment.⁹

Questionnaires were prepared in Arabic language, questions 1–8 are answered by (yes) or (no), in questions 1–4, 7, and 8, the answer (yes) gives 0 point and (no) gives 1 point. In questions 5–6, the answer (yes) gives 1 point and (no) gives 0 point. Question 9 is answered by: Never/rarely (5 points), once in a while (4 points), sometimes (3 points), usually (2 points) and all time (1 point). With scores ranging from 1–13, Patients scoring 11 or above in the summary score were classified as adherent as shown in (Table 1).^{10,11}

Imatinib Mesylate Adherence in Chronic Myeloid Leukemia Patients: Data from Middle Euphrates Region of Iraq

took it?	
4. Do you sometimes miss to bring along your medication when you travel or leave home?	Yes/No
5. Did you take your medicine yesterday?	Yes/No
6. Do you have a special routine or reminder system to help you take your medications?	Yes/No
7. Do you sometimes stop taking your medication if it feels like your disease is under control?	Yes/No
8. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	Yes/No
9. How often do you have difficulty remembering to take all of your medicines?	Scale 1-5

Response was evaluated up by measuring of *BCR-ABL1* transcription level in peripheral blood, that done as part of the clinical protocol and the findings were reported on the health information system of hospital regularly. All patients were personally interviewed during their routine follow up and their demographic data were also collected. Patients with non-conclusive results were excluded from our study. This study was approved by review ethical committee of Karbala teaching hospital, Iraq.

Data were analyzed by using the Social Sciences of Statistical Package (SPSS) version 20, Chi square procedure was being used to identify the significant differences at the level of significance ≤ 0.05 .

Results

There were 67 patients enrolled in our study, median age was 45 years and range (6-90) years. Thirty-four patients (50.75%) were male and 33 patients (49.25%) were female with M:F ratio 1.03:1. From those patients 56 patients (83.50%) were married and 11 patients (16.50%) were single. Majority of our patients had an educational level of primary school in 27 patients (40.30%) followed by secondary school in 18 patients (26.87%), higher education in 14 patients (20.89%) and 8 patients (11.94%) were Illiterates.

Chronic phase was the most common presenting phase in 63 patients (94.03%) followed by accelerated phase in 3 patients

(4.48%) and blast crisis in 1 patient (1.49%) as shown in (Table 2).

Table 2. Demographic features of the 67 patients.

Variable	N (%)
Gender	
Male	34 (50.75%)
Female	33 (49.25%)
Marital status	
Married	56 (83.50%)
Single	11 (16.50%)
Level of education	
Illiterate	8 (11.94%)
Primary	27 (40.30%)
Secondary	18 (26.87%)
Higher education	14 (20.89%)
Clinical presentation at diagnosis	
Chronic phase	63 (94.03%)
Accelerated Phase	3 (4.48%)
Blast crisis	1 (1.49%)

The overall mean Morisky score of 67 patients was 8.41, range was (3-13). Of the 67 patients, 18 patients (26.87%) were adherents, and 49 patients (73.13%) were non-adherent (Figure 1).

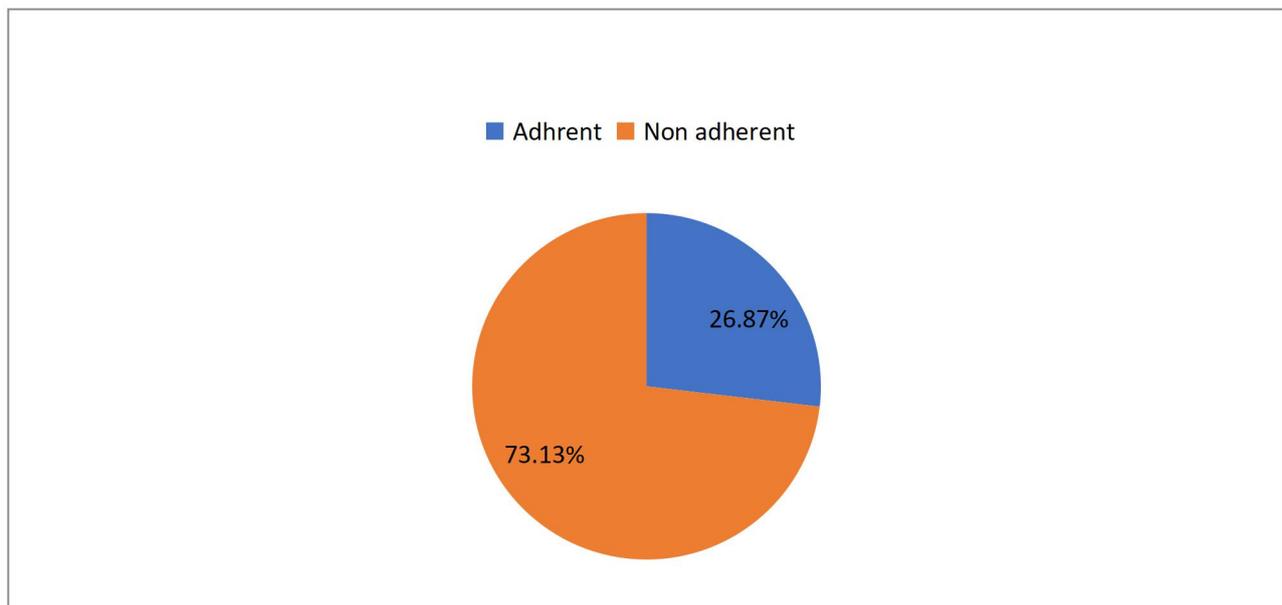
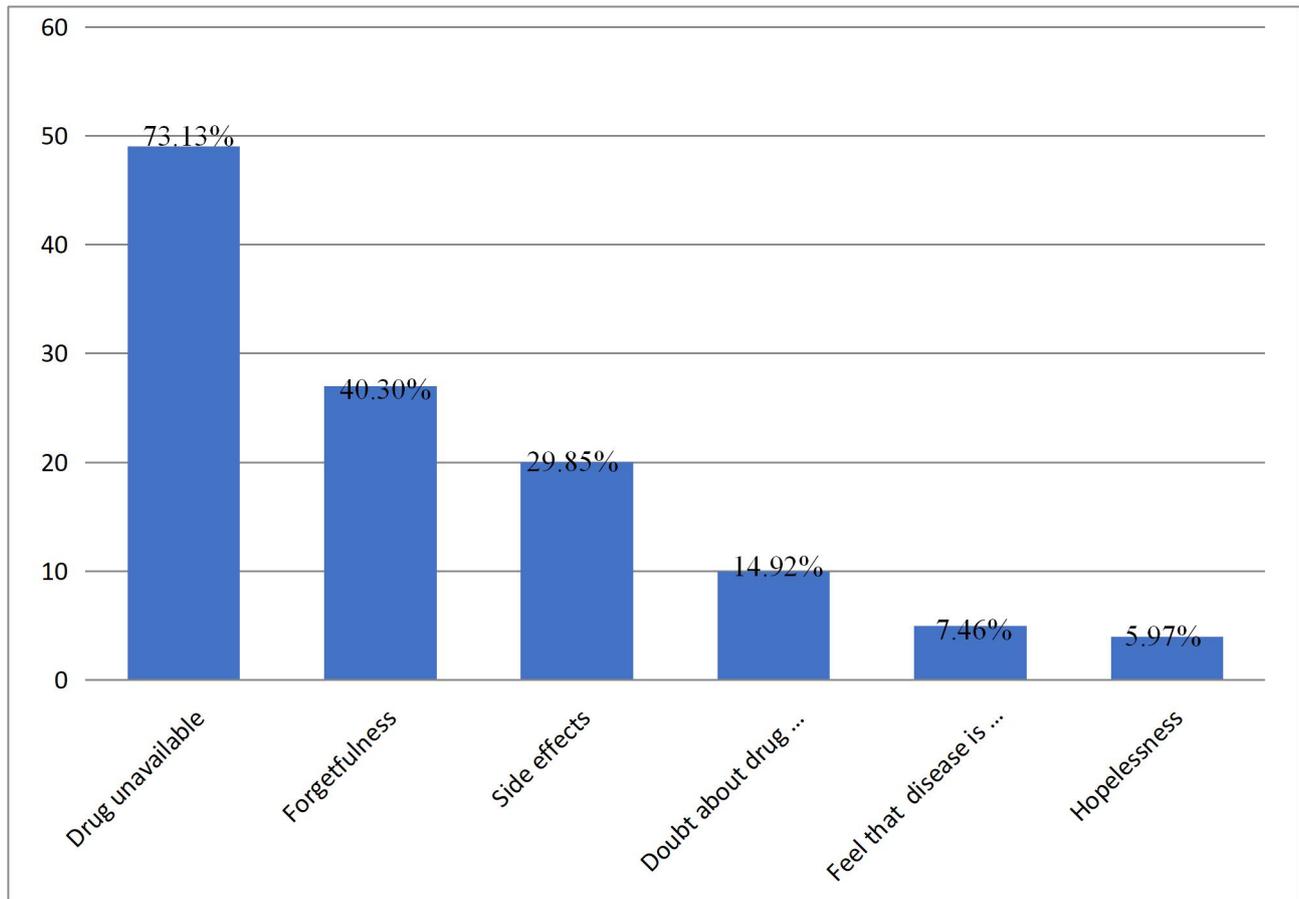


Figure 1. Patients adherence according to 9-items MMAS.

Imatinib Mesylate Adherence in Chronic Myeloid Leukemia Patients: Data from Middle Euphrates Region of Iraq

The most common cause for poor adherence in our patients was unavailability of drugs in 49 patients (73.13%) followed by forgetfulness in 27 patients (40.30%), side effects in 20

(14.92%), patients feel their disease is under control in 5 patients (7.46%) and hopelessness in 4 patients (5.97%) as shown in (Figure 2).



patients (29.85%), doubt about drug efficacy in 10 patients

Figure 2. Causes of non-adherence to imatinib.

Stomach pain & gastric upset was the most common side effects in 19 patients (28.36%) followed by joint pain in 16

patients (23.88%), muscle pain in 13 patients (19.40%), nausea in 13 patients (19.40%) and vomiting in 10 patients (14.92%), other side effects are shown in (Table 3).

Table 3. Side effects due to imatinib intake.

Side effects	N (%)
Fatigue	1 (1.49%)
Edema	6 (8.95%)
Nausea	13 (19.40%)
Diarrhea	2 (2.98%)
Vomiting	10 (14.92%)
Headache	7 (10.45%)
Drowsiness & Dizziness	8 (11.94%)
Nervousness	3 (4.48%)
Weight gain	4 (5.97%)
Allergy & Rash	1 (1.49%)
Fever	3 (4.48%)
Stomach pain & gastric upset	19 (28.36%)
Muscle pain	13 (19.40%)
Joint pain	16 (23.88%)
Abdominal pain	7 (10.45%)

There was no correlation between adherence and sex, level of education, marital status or side effects, but adherent patients were more likely to achieve optimal response in 83.3% of

patients comparing to 46.94% among non-adherence (P value =0.007; 95% CI: 1.45-22.04) as shown in (Tables 4 & 5).

Table 4. Categorical variables comparison with adherence using the 9-items MMAS.

Variable	Class of Adherence	Total	P value
----------	--------------------	-------	---------

Imatinib Mesylate Adherence in Chronic Myeloid Leukemia Patients: Data from Middle Euphrates Region of Iraq

		Non-adherent N (%)	Adherent N (%)		
Sex	Female	23 (69.70%)	10 (30.30%)	33 (100%)	0.531
	Male	26 (76.47%)	8 (23.53%)	34 (100%)	
Level of education	Illiterate to secondary school	38 (71.70%)	15 (28.30%)	53 (100%)	0.605
	Higher education	11 (78.57%)	3 (21.43%)	14 (100%)	
Marital status	No	7 (63.64%)	4 (36.36%)	11 (100%)	0.436
	Yes	42 (75.00%)	14 (25.00%)	56 (100%)	
Side effects	Yes	49 (73.13%)	18 (26.87%)	67 (100%)	0.470
	No	0 (0.00%)	(0.00%)	(0.00%)	

Table 5. Patients response according to adherence status.

Adherence	Response		Total	P value	Odds Ratio (95%CI)
	Optimal N (%)	Failure N (%)			
Adherent	15 (83.33%)	3 (16.67%)	18 (100%)	0.007*	5.65 (1.45-22.04)
Non-adherent	23 (46.94%)	26 (53.06%)	49 (100%)		

* means significant differences ($P \leq 0.05$).

Discussion

Leukemia accounts for more than 6% of cancer patients in Middle Euphrates region of Iraq, while CML represents more than 24% of leukemia cases in this region.^{12,13} Poor compliance to treatment had negative impact on CML patients, understanding factors that lead to in-compliance may help to improve treatment outcomes and decrease complications.^{14,15}

Only 26.87% of our patients were adherent, our results were much lower than in Qatar 69%, Sweden 97.36%, India 75%, Ethiopia 55.5% and Taiwan 73.1%.^{11,16-19} Drug unavailability was the major factor for non-compliance in 73.13% of our patients. Because of the long-term use of costly imatinib, the expense of treatment with CML has increased and now CML has been one of the most expensive illness.²⁰ Unavailability of drugs was also the main cause of poor adherence in Qatar and Brazil.^{11,21} While side effects were the main factor in UK, Ethiopia and Taiwan.^{18,19,22}

In our study there was no effect of sex, level of education, marital status and side effects on adherence, same result in India and Brazil.^{17,21} Although Darkow et al., showed that lack of adherence was greater among women.²³ While Marin et al. found that adherence was lower in younger patients and those who developed side effects.⁵

Adherent patients tend to achieve optimal response comparing to non-adherence, this was proved in studies in UK, Brazil, Taiwan and Belgium where the adherence rate and the molecular response were closely correlated.^{5,19,21,24}

Conclusion

This is first study to assess adherence to imatinib in Iraq, patient's adherence was very poor in our region. There was no correlation between adherence and sex, level of education, marital status or side effects. Unfortunately, drug unavailability was the major cause of non-adherence. The most common side effect in our patients was gastric upset. Adherent patients tend to achieve optimal response comparing to non-adherence. This result highlights the need for future studies in other parts of Iraq with larger numbers of patients to assess other possible factors for poor adherence. Health authority are advised to pay attention to the factors found in this study, that might help to improve treatment outcomes among CML patients in our country.

References

1. Faderl S, Talpaz M, Estrov Z, et al. The biology of chronic myeloid leukemia. *N Engl J Med.* 1999 Jul 15;341(3):164-72.
2. Lugo TG, Pendergast AM, Muller AJ, et al. Tyrosine kinase activity and transformation potency of ber-abl oncogene products. *Science.* 1990 Mar

2;247(4946):1079-82.

3. Pinheiro PS, Callahan KE, Siegel RL, et al. Cancer mortality in Hispanic ethnic groups. *Cancer Epidemiol Biomarkers Prev.* 2017 Mar 1;26(3):376-82.
4. An X, Tiwari AK, Sun Y, et al. BCR-ABL tyrosine kinase inhibitors in the treatment of Philadelphia chromosome positive chronic myeloid leukemia: a review. *Leuk Res.* 2010 Oct 1;34(10):1255-68.
5. Marin D, Bazeos A, Mahon FX, 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 May 10;28(14):2381.
6. Vermeire E, Hearnshaw H, Van Royen P, et al. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther.* 2001 Oct 30;26(5):331-42.
7. Benjamin RM. Medication adherence: helping patients take their medicines as directed. *Public Health Rep.* 2012 Jan;127(1):2-3.
8. Mjali A, Jawad SA, Al Baroodi BN. Gynecological Cancer in Middle Euphrates Region of Iraq, 2012-2020. *Asian Pac Environ Cancer.* 2020 Jun 4;3(1):17-8.
9. de Oliveira-Filho AD, Morisky DE, Neves SJ, et al. The 8-item Morisky Medication Adherence Scale: validation of a Brazilian-Portuguese version in hypertensive adults. *Res Social Adm Pharm.* 2014 May 1;10(3):554-61.
10. De las Cuevas C, Peñate W. Psychometric properties of the eight-item Morisky Medication Adherence Scale (MMAS-8) in a psychiatric outpatient setting. *Int J Clin Health Psychol.* 2015 May 1;15(2):121-9.
11. Al-Dewik NI, Morsi HM, Samara MM, et al. Is adherence to imatinib mesylate treatment among patients with chronic myeloid leukemia associated with better clinical outcomes in Qatar? *Clin Med Insights Oncol.* 2016 Jan;10: CMO-S32822.
12. Mjali A, Al Baroodi BN. Some Facts About Cancers in Karbala province of Iraq, 2012-2020. *Asian Pac J Cancer Care.* 2020 Jun 7;5(2):67-9.
13. Mjali A, Al-Shammari HH, Abbas NT, et al. Leukemia Epidemiology in Karbala province of Iraq. *Asian Pac J Cancer Care.* 2019;4(4):135-9.
14. Mjali A, Kareem YA, Al-Shammari HH, et al. Chronic myeloid leukemia patient with isolated central nervous system blast crisis. *World J Pharm Pharm Sci.* 2019;8(9): 111-117.
15. Mjali A, Hasan DM, Al-Anssari MJ, et al. Myeloid sarcoma as the presenting symptom of chronic myeloid leukemia chronic phase: A case report. *World J Pharm Res.* 2017; 6 (13): 10-15.
16. Jönsson S, Olsson B, Söderberg J, et al. Good adherence

Imatinib Mesylate Adherence in Chronic Myeloid Leukemia Patients: Data from Middle Euphrates Region of Iraq

- to imatinib therapy among patients with chronic myeloid leukemia—a single-center observational study. *Ann Hematol*. 2012 May 1;91(5):679-85.
17. Kapoor J, Agrawal N, Ahmed R, et al. Factors influencing adherence to imatinib in Indian chronic myeloid leukemia patients: a cross-sectional study. *Mediterr J Hematol Infect Dis*. 2015;7(1).
 18. Mulu Fentie A, Tadesse F, Engidawork E, et al. Prevalence and determinants of non-adherence to Imatinib in the first 3-months treatment among newly diagnosed Ethiopian's with chronic myeloid leukemia. *PloS one*. 2019 Mar 7;14(3): e0213557.
 19. Chen TC, Chen LC, Huang YB, Chang CS. Imatinib adherence associated clinical outcomes of chronic myeloid leukemia treatment in Taiwan. *Int J Clin Pharm*. 2014 Feb 1;36(1):172-81.
 20. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood*. 2013 May 30;121(22):4439-42.
 21. Reis SR, Quixada AT, Nunes ST, et al. Adherence to treatment with imatinib in chronic myeloid leukemia: a study of the first decade of responses obtained at a Brazilian hospital. *Rev Bras Hematol Hemoter*. 2013 Jun;35(3):174-9.
 22. Eliasson L, Clifford S, Barber N, et al. Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. *Leuk Res*. 2011 May 1;35(5):626-30.
 23. Darkow T, Henk HJ, Thomas SK, et al. Treatment interruptions and non-adherence with imatinib and associated healthcare costs. *Pharmacoeconomics*. 2007 Jun 1;25(6):481-96.
 24. Noens L, Van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of non-adherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood*. 2009 May 28;113(22):5401-11.