Original Article

Access this article online

Quick Response Code:

Website: https://journals.lww.com/ijhm

DOI: 10.4103/ijh.ijh_129_24

Eligibility for treatment-free remission among chronic myeloid leukemia patients in Iraqi Kurdistan region

Haydar Hasan Darwes[1,2], Ahmed K. Yassin[1,2], Rawand P. Shamoon[3,4,5]

Abstract:

BACKGROUND: The advent of tyrosine kinase inhibitors (TKIs) has significantly improved the survival rates of patients with chronic myeloid leukemia (CML) patients. The frequent side effects of TKIs have necessitated the need for a new approach. Treatment-free remission (TFR) has become a key goal in CML management, allowing eligible patients who meet specific criteria to safely discontinue TKI therapy.

OBJECTIVES: The objectives of this study were to identify CML patients on TKI therapy who are eligible for TFR, compare the clinical and hematological parameters among eligible and ineligible patients, and explore the reasons for patients' willingness or reluctance to pursue TFR.

PATIENTS AND METHODS: This retrospective study reviewed 129 accessible medical records of CML patients in three hemato-oncology centers in Iraqi Kurdistan between 2008 and 2024. Eligibility for TFR was assessed based on local criteria aligned with international guidelines, and eligible patients were compared to ineligible ones.

RESULTS: Files of 129 CML patients on TKI therapy were reviewed. Their median age at diagnosis was 46 years. Only 8.5% of the patients were eligible for TFR. Ineligibility was primarily due to insufficient TKI treatment (41.6%), inadequate deep molecular response (17.5%), and lack of regular molecular follow-up (40.6%). While patients expressed their desire to discontinue TKI to avoid side effects and reduce compliance, reluctance stemmed from fear of relapse and the unavailability of newer generation TKIs in case of the development of resistant mutations.

CONCLUSIONS: A minority of CML patients in our region were eligible for TFR. Ineligibility for TFR was mainly due to insufficient TKI therapy and irregular molecular monitoring.

Keywords:

Chronic myeloid leukemia, Iraqi Kurdistan, treatment-free remission, tyrosine kinase inhibitors

Departments of [1]Internal Medicine and [3]Pathology, College of Medicine, Hawler Medical University, [2]Department of Clinical Hematology, Nanakali Hospital, [4]Department of Hematopathology, Nanakali Hospital, [5]Department of Preclinical Sciences, Division of Pathology, School of Medicine, University of Kurdistan Hawler, Erbil, Iraq

Address for correspondence:
Dr. Haydar Hasan Darwes, Department of Internal Medicine, College of Medicine, Hawler Medical University, Erbil, Iraq.
E-mail: haydar.husain@gmail.com

Submission: 16-11-2024
Revised: 08-12-2024
Accepted: 15-12-2024
Published: 24-04-2025

Introduction

Since Virchow and Binnette first described chronic myeloid leukemia (CML) in the mid-1980s,[1] significant progress has been made in understanding its cytogenetic and molecular features. One of the most important discoveries was the BCR-ABL1 gene rearrangement, which leads to unregulated tyrosine kinase activity responsible for cell transformation.[2,3] This key finding paved the way for the development of tyrosine kinase inhibitors (TKIs). Imatinib, the first TKI, dramatically improved survival rates for CML patients, bringing overall survival closer to that of the general population.[4]

The improved survival rates in CML have led to an increased prevalence of the disease, which in turn has heightened the cost and burden on the healthcare system.[5] In addition, TKI therapy is often linked to adverse effects that can affect patients' quality of life. Common side effects include fatigue, nausea, depression, sleep disturbances, diarrhea, pain, fluid retention, and skin issues. With longer follow-up,

How to cite this article: Darwes HH, Yassin AK, Shamoon RP. Eligibility for treatment-free remission among chronic myeloid leukemia patients in Iraqi Kurdistan region. Iraqi J Hematol 2025;14:37-41.

other side effects have also been identified, such as pulmonary hypertension in patients on dasatinib and peripheral arterial occlusive disease and hyperglycemia and hyperlipidemia in patients on nilotinib.[6]

Initially, lifelong TKI treatment was recommended for CML patients. However, clinical trials have consistently shown that many can maintain molecular responses even after stopping TKI therapy.[7-9] Treatment-free remission (TFR) has now become the new goal in managing chronic CML. Studies have demonstrated that around 50% of patients who achieved a deep molecular response (DMR) with imatinib or second-generation TKIs such as dasatinib or nilotinib can safely and successfully achieve TFR.[7,10] The reasons why some patients sustain TFR while others do not remain uncertain, though immune factors are believed to contribute to the suppression of leukemic clones and stem cells.[11] Notably, all trials have demonstrated that patients who relapse after discontinuing TKI therapy respond promptly upon restarting it, without the emergence of new mutations or progression of the disease. It is prudent to inform CML patients that TFR may last from a few months to many years, and approximately 20% may never need to resume TKI therapy.[12]

The probability of achieving successful TFR in CML patients may increase with longer durations of TKI therapy and deeper molecular responses. However, factors such as younger age, high Sokal scores, and TKI resistance may indicate a higher risk of TFR failure.[13,14] Patients considering TFR often do so to avoid undesirable side effects, reduce the risk of potential long-term complications, alleviate the inconvenience of daily medication, and lower treatment costs. Despite the proven safety of TFR, less than half of eligible patients are willing to discontinue TKI therapy. Their reluctance is often due to concerns about disease recurrence, side effects, and the possibility of experiencing TKI withdrawal syndrome.[11,15,16]

The aim of this study is to identify CML patients in Kurdistan region of Iraq who are eligible for cessation of TKIs, to compare the clinical and hematological characteristics of eligible and ineligible patients to identify potential predictive factors for eligibility, and to explore the reasons behind eligible patients' willingness or reluctance to adopt TFR.

Patients and Methods

This retrospective study was carried out in the three hemato-oncology centers in Iraqi Kurdistan region: Nanakali Hospital in Erbil, Hiwa Hospital in Sulaymaniyah, and Azadi Hematology-Oncology Center in Duhok. Out of the 530 registered CML patients who visited these hospitals from 2008 to 2024, only 129 had assessable medical records, which were subsequently reviewed. The enrolled patients received either the first-generation TKI (imatinib) or a second-generation TKI (either dasatinib, nilotinib, or bosutinib). This study was approved by the ethical committee of the author's institution. Verbal informed consent was obtained from all participants before their inclusion.

Information regarding the patient's age, gender, clinical presentation, hematological parameters, cytogenetic findings, and treatment regimens was collected. The Sokal prognostic index was calculated.[17] CML patients were deemed eligible for TFR if they met the following local criteria, aligned with European and Latin American recommendations:[18,19]

1. Patients in the first chronic phase
2. Access to high-quality quantitative polymerase chain reaction (PCR) using the international scale with quick turnaround times for test results
3. Patient agreement to more frequent monitoring after discontinuing treatment, with monthly testing for the first 6 months, every 2 months between months 6 and 12, and every 3 months thereafter
4. First-line therapy or second-line therapy if the change was solely due to intolerance
5. Duration of TKI therapy exceeding 5 years (or more than 4 years for second-generation TKIs)
6. Duration of DMR (DMR4 or better) exceeding 2 years.

The characteristics of eligible patients were then compared to the remaining ineligible patients. Patients were then contacted, informed about the TFR, and asked whether they were willing to adopt the regimen. They were also asked to provide reasons for their willingness or reluctance.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 26) (IBM®, Michigan, Illinois, USA). The Chi-square test was employed to compare the proportions between two or more groups, whereas Fisher's exact test was applied when more than 20% of the table cells had an expected frequency of < 5. $P \leq 0.05$ was considered statistically significant.

Results

The files of 129 patients were reviewed, consisting of 69 males and 60 females, with a male-to-female ratio of 1.15:1. The median age of the patients was 52 years, while their median age at diagnosis was 45 years. The majority of patients (46%) were in the 40–59 years of age group. Most of the patients were from Erbil (65.7%), followed by Sulaymaniyah (22.6%) and Duhok (11.7%).

At the time of diagnosis, 60.6% of the patients were anemic (n = 66), 63.3% had a white blood cell (WBC)

count exceeding 100 × 10^9/L (n = 69), and 84.1% had splenomegaly (n = 90). Regarding the Sokal risk score, 48.1% had a low risk (n = 39), while 43.2% (n = 35) had an intermediate risk, and 8.6% (n = 7) had a high risk.

Nearly all patients (98.1%) achieved complete hematological response (CHR), with 38.5% responding within the first 3 months of therapy. Major molecular response (MMR) was attained by 74.5% of patients, while only 43% reached DMR. The details of age at diagnosis are shown in Table 1.

The proportion of patients eligible for TFR was 8.5%. None of the patients aged 60 or older were eligible, compared to 12.7% of those aged 40–49 years and 9.4% of those under 40 years (P = 0.029). There was no significant association between eligibility and gender (P = 0.587). A significant association was found between TFR and age at diagnosis (P = 0.030), as none of the patients diagnosed at 50 years or older were eligible [Table 2].

No significant associations were found between TFR eligibility and the following variables: spleen size (P = 0.122), anemia (P = 0.737), WBC count (P = 0.320), platelets (P = 0.711), blasts (P = 0.720), basophils (P = 1.000), and Sokal score (P = 0.126). Similarly, there were no significant associations between eligibility and treatment-related or milestone variables, including CHR (P = 0.745), MMR (P = 0.820), and TKI agents (P = 0.472) [Table 3].

Table 1: Chronic myeloid leukemia patient age at diagnosis

	n (%)
Age at diagnosis (*n*=129)	
<30	17 (13.1)
30–49	65 (50.4)
50–69	42 (32.6)
≥70	5 (3.9)
Total	129 (100.0)

The primary reasons for ineligibility were insufficient duration of TKI therapy (41.6%), inadequate duration of DMR (17.4%), and lack or irregularity of molecular monitoring (40.8%).

Among the 129 patients, only 11.6% (15 patients) were willing to pursue TFR. In addition, 30.2% would consider TFR if molecular testing were provided free of charge, 20.9% were hesitant, and 35.7% could not be reached. The main reasons for reluctance were the risk of relapse and the financial burden (63%). Further details are found in Table 4.

Discussion

CML is a common hematological malignancy in the Kurdistan region of Iraq, accounting for about 20% of all leukemia cases in the area.[20] TFR is becoming an increasingly sought-after goal for CML patients in DMR, driven by the burden of symptoms, costs, and potential toxicities linked to long-term TKI therapy. While TFR should be considered the ultimate objective for these patients, many eligible individuals remain hesitant to discontinue TKIs when given the chance despite the numerous compelling reasons to do so.[5,11]

In the current cohort, the median age at diagnosis of the studied patients was 46 years, which aligns closely with reports from other studies conducted in Kurdistan region and Iraq.[12,21] However, this age is approximately 10 years younger than what has been reported in western countries. As observed in other studies, a slight predominance of male patients was noted in this series.[22-24] The clinical presentation of CML in this study was typical; however, the incidence of anemia and splenomegaly was higher than in western countries, where about 50% of cases are discovered incidentally through routine blood tests.[23] This difference is likely due to screening programs,

Table 2: Eligibility by age, sex, and age at diagnosis

	Eligibility for treatment-free remission		Total	*P*
	Eligible	Not Eligible		
Age (years)				
<40	3 (9.4)	29 (90.6)	32 (100.0)	
40-59	8 (12.7)	55 (87.3)	63 (100.0)	
≥60	0 (0.0)	42 (100.0)	42 (100.0)	0.029**
Sex				
Male	5 (6.8)	68 (93.2)	73 (100.0)	
Female	6 (9.4)	58 (90.6)	64 (100.0)	0.587*
Age at diagnosis (years)				
<30	3 (17.6)	14 (82.4)	17 (100.0)	
30-49	8 (12.3)	57 (87.7)	65 (100.0)	
50-69	0 (0.0)	42 (100.0)	42 (100.0)	
≥70	0 (0.0)	5 (100.0)	5 (100.0)	0.030**
Total	11 (8.5)	118 (91.5)	129 (100.0)	

*Calculated by the Chi-square test. **Calculated by Fisher's exact test

Table 3: Treatment-free remission eligibility by response milestones and tyrosine kinase inhibitors

	Eligible, *n* (%)	Not eligible, *n* (%)	Total, *n* (%)	*P*
CHR in months				
<3	5 (13.5)	32 (86.5)	37 (100.0)	0.745**
≥3	6 (10.2)	53 (89.8)	59 (100.0)	
Total achievers of CHR	11 (11.5)	85 (88.5)	96 (100.0)	
MMR (months)				
<12	5 (14.3)	30 (85.7)	35 (100.0)	0.820*
≥12	6 (16.2)	31 (83.8)	37 (100.0)	
Total achievers of MMR	11 (15.3)	61 (84.7)	72 (100.0)	
TKI				
First generation	7 (7.3)	89 (92.7)	96 (100.0)	0.472**
Second generation	4 (12.1)	29 (87.9)	33 (100.0)	
Total	11 (8.5)	118 (91.5)	129 (100.0)	

*Calculated by the Chi-square test, **Calculated by Fisher's exact test. MMR=Major molecular response, CHR=Complete hematological response, TKI=Tyrosine kinase inhibitors

Table 4: Attitude of patients to treatment-free remission

	n (%)
Willing to adopt TFR	15 (11.6)
Reluctant	27 (20.9)
Conditioned willing	39 (30.2)
Unreachable	46 (35.7)
Death	2 (1.6)
Total	129 (100.0)
Causes of reluctance	
Risk of relapse	9 (33.3)
Risk of relapse and financial burden	17 (63.0)
Already tried and failed	1 (3.7)
Total	27 (100.0)

TFR=Treatment-free remission

preemployment testing, and better health education in those countries, leading to earlier diagnosis. In this study, while the majority of patients achieved CHR and MMR, only a small portion of patients were eligible for TKI discontinuation (11 patients, 8.5%). CHR is defined as the normalization of blood counts, splenomegaly, and resolution of constitutional symptoms, while MMR and DMR are defined as 3 log and 4 or more log reductions in BCR-ABL1 transcripts by PCR testing, respectively. Molecular testing is performed through standardized PCR technique. The main reasons for ineligibility to stop TKIs included inadequate molecular monitoring, limited testing availability in government centers, and the high cost of testing in private laboratories. Currently, our CML patients are performing cytogenetic and molecular testing at private laboratories, which is costly, especially when frequent testing is required after TKI discontinuation.

In this cohort, there was a significant association between the patient's age and age at diagnosis with eligibility to stop TKIs ($P < 0.05$ and 0.02, respectively). Patients aged between 40 and 60 years had a higher chance of being eligible compared to elderly or very young patients. No association was found between the other hematological and clinical parameters and eligibility status; although the mean Sokal score of ineligible patients was higher than that of eligible ones, the difference did not reach statistical significance, likely due to the small number of eligible patients in this study. Certain factors, such as the duration of TKI therapy, depth of molecular response, and Sokal score at diagnosis,[14] are reported to be important for determining eligibility and the probability of successful TFR. However, we did not observe a significant impact of these factors in our study, a conclusion that is consistent with findings from other researchers who also failed to demonstrate a significant effect of these variables.[12,25]

Many eligible patients were willing to discontinue TKI therapy after being reassured about the safety of the approach. The primary motives for stopping treatment were drug side effects and the high cost of molecular testing. However, concerns about the high cost of frequent molecular testing initially, estimated at $1350 during the 1st year of TFR and $600 annually thereafter,[26] and the fear of relapse were the main reasons for reluctance. Raising patient awareness about the safety and benefits of TFR, along with educating them on the importance of regular molecular assessments and providing free molecular testing, would motivate more patients to consider the option of TFR.

Conclusions

CML patients in the Kurdistan region tend to be younger, with higher WBC counts and a higher rate of splenomegaly at diagnosis. Despite achieving a rapid CHR with TKIs, the number of patients eligible for TFR was limited, mainly due to irregular molecular monitoring. Apart from age, eligibility was not linked to clinical parameters at diagnosis. Most patients were willing to pursue TFR to avoid side effects and the high cost of molecular testing, while reluctance was mainly due to fear of relapse and the high cost of frequent molecular testing after stopping TKIs.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Bennett JH. Case of hypertrophy of the spleen and liver, which death took place from suppuration of the blood. Edin Med Surg J 1845;165:1812-45.
2. Heisterkamp N, Stephenson JR, Groffen J, Hansen PF, de Klein A, Bartram CR, *et al.* Localization of the c-ab1 oncogene adjacent to a translocation break point in chronic myelocytic leukaemia. Nature 1983;306:239-42.
3. Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. Science 1990;247:824-30.
4. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol 2016;34:2851-7.
5. Han JJ. Treatment-free remission after discontinuation of imatinib, dasatinib, and nilotinib in patients with chronic myeloid leukemia. Blood Res 2023;58:S58-65.
6. Mughal TI, Schrieber A. Principal long-term adverse effects of imatinib in patients with chronic myeloid leukemia in chronic phase. Biologics 2010;4:315-23.
7. Mahon FX, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, *et al.* Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: The prospective, multicentre stop imatinib (STIM) trial. Lancet Oncol 2010;11:1029-35.
8. Ross DM, Branford S, Seymour JF, Schwarer AP, Arthur C, Yeung DT, *et al.* Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: Results from the TWISTER study. Blood 2013;122:515-22.
9. Etienne G, Guilhot J, Rea D, Rigal-Huguet F, Nicolini F, Charbonnier A, *et al.* Long-term follow-up of the French stop imatinib (STIM1) study in patients with chronic myeloid leukemia. J Clin Oncol 2017;35:298-305.
10. Aleem A, Alqahtani F, Jamal A, Alkhudair NA, Alghafis M, Siti HW, *et al.* Discontinuation of tyrosine kinase inhibitor therapy and treatment-free remission in chronic-phase chronic myeloid leukemia: An observational retrospective multi-center study. Blood 2022;140:12220-1.
11. Atallah E, Sweet K. Treatment-free remission: The new goal in CML therapy. Curr Hematol Malig Rep 2021;16:433-9.
12. Jumaa AK, Khalaf AA, Hasson HM, Dawood QM, Qasim ZR. Treatment-free remission in chronic myeloid leukemia (CML): Experience of Basrah haematology Centre. Oncol Radiother 2022;16:17-9.
13. Costa A, Breccia M. How to improve treatment-free remission eligibility in chronic myeloid leukaemia? Br J Haematol 2024;204:434-48.
14. Ahmed K, Iftikhar R, Iqbal Z, Arshad M, Ahmed A. Treatment free remission in chronic myeloid leukemia; a practical option. J Haematol Stem Cell Res 2023;3:32-40.
15. Goldberg S, Hamarman S. Patients with chronic myelogenous leukemia may not want to discontinue tyrosine kinase inhibitor therapy. Blood 2015;126:1584.
16. Sharf G, Marin C, Bradley JA, Pemberton-Whiteley Z, Bombaci F, Christensen RI, *et al.* Treatment-free remission in chronic myeloid leukemia: The patient perspective and areas of unmet needs. Leukemia 2020;34:2102-12.
17. Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, *et al.* Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-99.
18. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, *et al.* European leukemianet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020;34:966-84.
19. Pavlovsky C, Abello Polo V, Pagnano K, Varela AI, Agudelo C, Bianchini M, *et al.* Treatment-free remission in patients with chronic myeloid leukemia: Recommendations of the LALNET expert panel. Blood Adv 2021;5:4855-63.
20. Karim ZA, Khidhir KG, Ahmed RA, Hassan HA, Karim DO. Leukemia study in Sulaymaniyah province, Kurdistan, Iraq. Chin Med J (Engl) 2016;129:244-5.
21. Hasan KM. Evaluation of chronic myeloid leukemia patients and their molecular responses to tyrosine kinase inhibitors in Erbil city, Iraq. Iraqi J Hematol 2018;7:1-7.
22. Hoffmann VS, Baccarani M, Hasford J, Lindoerfer D, Burgstaller S, Sertic D, *et al.* The EUTOS population-based registry: Incidence and clinical characteristics of 2904 CML patients in 20 European countries. Leukemia 2015;29:1336-43.
23. Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. The biology of chronic myeloid leukemia. N Engl J Med 1999;341:164-72.
24. Eissa AA, Hasan AM, Sulaiman DM. Clinico-pathological profile of patients with chronic myeloid leukemia from Duhok/Iraq. Duhok Med J 2016;10:47-53.
25. Gesiotto QJ, Jain AG, Ball S, Nodzon L, Rodriguez A, Komrokji RS, *et al*. Treatment Free Remission in Patients with Chronic Phase CML: A Single Center Experience. Blood 2021;138:3612.
26. Bourne G, Bhatia R, Jamy O. Treatment-free remission in chronic myeloid leukemia. J Clin Med 2024;13:2567.