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Discontinuation of Tyrosine Kinase Inhibitor Therapy and Treatment Free Remission (TFR) in Chronic Myeloid Leukemia: Successful Achievement of TFR in More Than Two-Third of Patients in a Real-World Practice

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Highlights

- Discontinuation of TKI therapy and treatment-free remission (TFR) is a new goal for chronic-phase CML.
- Discontinuation of TKI therapy and successful TFR can be achieved in 40% to 60% of chronic-phase CML patients.
- Limited data exist on safety and outcomes of this approach from developing countries.
- Discontinuation of TKI therapy and successful TFR was safe and feasible in a real-world practice.
- Longer TKI therapy after deep molecular remission may achieve successful TFR in more than two-third of patients.

Discontinuation of Tyrosine Kinase Inhibitor Therapy and Treatment Free Remission (TFR) in Chronic Myeloid Leukemia: Successful Achievement of TFR in More Than Two-Third of Patients in a Real-World Practice

By

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Short running title: Discontinuation of TKI therapy and TFR in CML

Conflict of interest: The authors declare they have no competing financial interest related to this paper.

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Abstract:

Background: Discontinuation of TKI therapy and treatment-free remission (TFR) have become new goals for chronic-phase chronic myeloid leukemia (CP-CML). The aim of this study was to estimate the TFR post discontinuation of TKI therapy at three tertiary-care centers.

Patients and Methods: CP-CML patients aged ≥ 16 years who had an attempt to discontinue TKI therapy till June 2022, were eligible. The collected data included patients' demographics, prognostic score, type and duration of TKI therapy, response dates, relapse dates, response to re-initiation of TKI therapy, and risk factors for relapse.

Results: Fifty-five patients (35, 63.6% females) with a median age of 40 (range 16-74) years at diagnosis discontinued therapy. Forty-eight (87.3%) patients received imatinib as first line therapy. Twenty-nine (52.7%) patients were receiving imatinib at the time of TKI-discontinuation. Median time from diagnosis to TKI discontinuation was 86 months (IQR 60;132) and median duration of TKI therapy after achieving DMR was 66 months (IQR 47;114). After a median follow up of 34 (IQR 12;68) months, 15 (27.3%) patients relapsed. Median time to relapse was 5 months (range 2-38). Most of the relapses occurred during the first 6 months except 3 (20%) patients. All the relapsed patients achieved MMR after a median of 3 (range 2-6) months after restarting TKI therapy. None of the patients progressed to advanced-phase.

Conclusion: Our experience confirms that discontinuation of TKI therapy in CP-CML patients is feasible and safe in routine clinical practice, and can achieve TFR in more than two-third of carefully selected patients.

Key words: Chronic myeloid leukemia, discontinuation, therapy, treatment free remission, tyrosine kinase inhibitor

Introduction:

Tyrosine kinase inhibitors (TKI) have revolutionized the management of chronic myeloid leukemia (CML). Majority of the CML patients in chronic phase (CP) receiving TKI therapy achieve a major molecular response and expect to have a life expectancy quite similar to the general population (1,2). With the achievement of this success, attention has been focused on the long-term toxicity of TKI therapy.

Despite the success of TKIs in the management of CP-CML, their use is not without limitations. Although well tolerated, long-term TKI therapy can be associated with significant toxicity and symptom burden, leading to a compromised quality of life (3-5). There is increasing evidence that second- and third-generation TKIs can potentially cause significant morbidity and mortality (6,7). Moreover, the financial burden of lifelong TKI therapy can be substantial, both for the patients and the healthcare systems (8), and discontinuation of treatment may save significant amounts of money (9). As a result, considerable interest has emerged to explore the concept of discontinuation of therapy and treatment-free remission (TFR) for CP-CML patients. TFR, defined as the maintenance of a major molecular response (MMR) or better following TKI discontinuation, represents a new therapeutic goal that could alleviate some of the drawbacks associated with continuous TKI therapy (10).

The Stop Imatinib 1 (STIM1) study showed that after a median follow-up of almost 6 years, nearly 40% of patients maintained a DMR, and established the concept of treatment

discontinuation (11). Subsequent clinical trials have provided similar results with imatinib and second-generation TKIs demonstrating that around 40-60% of CP-CML patients can achieve durable TFR after TKI discontinuation, without experiencing molecular relapse or progression (12-22).

Although feasible, and being applied in clinical practice, real world experience with discontinuation of TKI therapy is still limited (23-27), particularly from the Middle East and the developing countries, and needs to be studied to explore the feasibility and safety of this approach. Moreover, it is also important to study different factors which may be associated with long term achievement of TFR or risk of relapse. Hence, the aim of this study was to assess the outcome of CP-CML patients who discontinued TKI therapy in routine clinical practice.

Patients and methods:

Patients' data collection: All patients aged ≥ 16 years diagnosed with CP-CML and treated at 3 tertiary care centers in Riyadh who had an attempt to discontinue TKI therapy to achieve TFR, were included. The centers which participated in this study included the Adult Departments of Hematology/Oncology at 1) King Khalid University Hospital, King Saud University, Riyadh; 2) King Fahad Medical City, Riyadh; and 3) King Abdulaziz Medical City, King Saud bin Abdulaziz University for Health Sciences, Riyadh. The criteria to stop therapy were according to the clinical Practice guidelines. Briefly, patients were required to have received TKI therapy for at least 24 months after achieving deep molecular response (DMR) i.e., BCR::ABL1 level of ≤ 0.01 (MR4) or better on international scale (IS). Patients who discontinued therapy because of pregnancy or toxicity were also eligible. The study was approved by the institutional review

boards of all the participating centers. The requirement for written informed consent was waived because of the retrospective nature of the study.

The collected data included demographic characteristics (gender, age), clinical characteristics i.e., prognostic score, SOKAL score, pre-TKI treatment (if any), type of TKIs used, duration of TKI therapy before discontinuation and type of molecular response, time to achieve major molecular response (MMR) after initiation of TKI therapy, relapse data including time to relapse and response to re-initiation of TKI therapy, and risk factors for relapse.

Study definitions: MMR was defined as 3-log reduction (MR3) of BCR::ABL1 to $\leq 0.1\%$, MR4 as 4-log reduction or BCR::ABL1 $\leq 0.01\%$, and MR4.5 as 4.5-log reduction or BCR::ABL1 $\leq 0.0032\%$, on IS. Complete molecular response (CMR) was defined as no detectable BCR::ABL1 transcripts. TFR duration was calculated as the time between the date of TKI cessation and the date of restarting TKI therapy, or in case of no relapse, the date of last follow up. Molecular relapse was defined as loss of major molecular response (BCR::ABL1 $> 0.1\%$). Criterion to restart TKI therapy in relapsed patients was loss of MMR (BCR::ABL1 $> 0.1\%$).

Statistical analysis: The categorical variables like gender and Sokal score were summarized using the frequency and percentages. The quantitative variables were summarized as mean and standard deviation, or median with ranges, and quartiles. Fisher exact test was used to assess the association of other variables with relapse. Wilcoxon's two-sample test was utilized for quantitative variables comparison.

Results:

Patient Characteristics: Fifty-five patients (35, 63.6% females) with a median age of 40 (range 16-74) years at diagnosis were included in the study. Median age at TKI discontinuation was 48 (range 21-80) years. Majority of the patients (48; 87.3%) received imatinib as the first line therapy and only 7 (12.7%) patients received a second generation TKI as initial therapy (dasatinib or nilotinib). Twenty-nine (52.7%) patients were receiving imatinib at the time of TKI-discontinuation, and 26 (47.3%) were receiving a second-generation TKI. The reasons to change imatinib to another (second generation) TKI were as follows: intolerance 8, resistance 4, and suboptimal response 7 patients. None of the patients received any pre-TKI treatment other than hydroxyurea as initial debulking therapy for short periods. Patients' characteristics are summarized in table 1.

Fifty-two (94.5%) patients discontinued TKI as per clinical practice (shared decision between the treating physician and the patient), and 3 (5.5%) stopped because of pregnancy; 2 patients remained in deep MR post-delivery and fulfilled the criteria to discontinue therapy so they were offered not to resume treatment. One patient who was in deep remission and stopped TKI therapy because of pregnancy, declined to restart TKI (dasatinib) after delivery although she had only 24 months of deep response, and continued to have deep remission after 91 months of follow up.

One male patient requested to restart TKI therapy during increasing BCR::ABL1 ratio but before the loss of MMR. He restarted the same TKI and achieved CMR promptly. He was included in the relapsed patients' group.

Median time to achieve MMR after diagnosis was 12 (IQR 3;24) months. Median time from diagnosis to TKI discontinuation was 86 months (IQR 60;132) and median duration of DMR and

duration of TKI therapy after achieving DMR was 66 months (IQR 47;114). All the patients had achieved and maintained CMR during TKI therapy before discontinuation.

Relapse data: After a median follow up of 34 months (IQR 12;68) post TKI-discontinuation, 15 (27.3%) patients relapsed with an overall TFR rate of 72.7% (Figure 1). Median time to relapse was 5 months (range 3-38). Most of the relapses occurred during the first 6 months except 3 patients who relapsed at 10, 11, and 38 months after TKI discontinuation. Characteristics of the relapsed patients are presented in table 2.

More patients with intermediate- and high-risk Sokal score relapsed as compared to low-risk patients but this difference was not statistically significant (table 3). We also analyzed relapse rate according to duration of DMR of ≥ 60 months compared with DMR of < 60 months, and it was not significant (table 3). All the relapsed patients achieved MMR after a median of 3 months (range 2-6) after restarting TKI therapy. The type of TKI resumed at the time of relapse was the same used at the time of discontinuation in all patients except one patient. None of the patients progressed to advanced phase.

Discussion:

Treatment free remission (TFR) has become an important goal in the management of CML. Although multiple clinical trials of TKI discontinuation in CML have been published, still the real-world data are scanty, particularly from outside of Western countries. It is important to study TFR in different patient populations to know the dynamics and outcome of TKI discontinuation. The results of the current study demonstrate that TKI discontinuation is feasible and safe in

routine clinical practice and TFR can be achieved in more than two-third of carefully selected patients.

Various factors found to be associated with the risk of relapse include high Sokal score, shorter period of deep remission prior to TKI discontinuation, some laboratory markers like subset of lymphocytes, and the type of BCR::ABL1 transcript (7,8,19,28-31). None of these factors has been consistently associated with the risk of relapse, possibly due to different characteristics of patients in these studies. We did not find any of the parameters analyzed to be associated with the risk of relapse. Although more patients with intermediate and high Sokal score relapsed, it was not statistically significant when compared to low-risk patients.

Deep molecular remission (DMR) and a longer duration of TKI therapy after achieving DMR have been some of the more consistent factors associated with achievement of higher TFR rates (32,33). Haddad et al reported that discontinuation of TKI therapy after a DMR of ≥ 5 years resulted in a 5-year TFR rate of $>80\%$ (32). A meta-analysis of 12 studies including ~1700 patients showed that trials with molecular criteria of MR4.5 or better for stopping TKI reported higher TFR rates than those of MR4.0 (57.2% vs. 50.5%). Moreover, trials with eligibility criteria of at least 24 months of DMR duration demonstrated higher TFR rates than those for 18 or 12 months (60.2% vs. 49.9%) (33). These reports indicate that a longer duration of DMR before TKI discontinuation, possibly more than 5 years, is likely to be associated with a higher probability of successful TFR. In the current study, majority of the patients had long duration of TKI therapy (median 66 months) after achieving DMR. Although, the above 2 factors were not significantly associated with achieving successful TFR, the most likely explanation of more than

two-third of our patients having successful TFR is the long duration of TKI therapy after achieving DMR in majority of the cases.

In view of the several clinical trials, the National Comprehensive Cancer Network (NCCN) guidelines recommend TKI therapy for at least 3 years and a stable molecular response ($\geq$ MR4) for ≥ 2 years to be used as the criteria to consider before attempting TFR (11-13,19,22,33-35). Our results reiterate that a longer duration of TKI therapy after achieving DMR can achieve successful TFR in more than two-third of patients (32-33,37). Moreover, some studies have shown no difference in the rate of TFR when imatinib was compared to second-generation TKIs (32). More than half of our patients were receiving imatinib at the time of discontinuation of therapy. Our observations along with others' (32-33, 40), may have important implications for CML patients in lower income countries receiving imatinib. Generic imatinib is cheaper and may be the only TKI available in some countries. Therefore, a number of CML patients who receive imatinib and achieve DMR, can expect to discontinue therapy and achieve successful TFR.

In line with the results of other studies (11-13,19-22,33-34,37), most of the patients who failed TFR in the current study, relapsed during the first 6 months after TKI discontinuation, although late relapses were seen in some patients. In published literature, majority of the CML patients who discontinued therapy, relapsed during the first year, though late relapses have also been reported (32-34, 37-38). The possibility of late relapses in some patients mandates long-term surveillance and follow up of these patients.

Although our study has the limitations of being retrospective and including smaller numbers, it does show that successful TFR can be achieved in more than two-third of patients with longer

duration of TKI therapy after achieving DMR. This study, along with some other studies (13,27,31,39), suggest that a longer duration of TKI therapy is likely to yield better results and may overcome some of the poor prognostic factors like high Sokal score (32).

Conclusion: Successful TKI discontinuation and TFR was achieved in more than two-thirds of carefully selected patients with longer duration of TKI therapy after achieving DMR. Despite the limitation of a retrospective study, our experience in this population confirms that discontinuation of TKI therapy in CP-CML patients is feasible and safe in routine clinical practice.

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References:

1. Bower H, Björkholm M, Dickman PW, Hoglund M, Lambert PC, Andersson TM-L. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. *J Clin Oncol*. 2016;34:2851-7.
2. Sasaki K, Strom SS, O'Brien S, Jabbour E, Ravandi F, Konopleva M, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. *Lancet Haematol* 2015; 2: e186-e193
3. Steegmann JL, Baccarani M, Breccia M, Casado LF, García-Gutiérrez V, Hochhaus A, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia*. 2016;30:1648-71.
4. Williams LA, Garcia Gonzalez AG, Ault P, Mendoza TR, Sailors ML, Williams JL, et al. Measuring the symptom burden associated with the treatment of chronic myeloid leukemia. *Blood* 2013; 122: 641-47.

5. Efficace F, Baccarani M, Breccia M, Alimena G, Rosti G, Cottone F, et al; GIMEMA. Health-related quality of life in chronic myeloid leukemia patients receiving long-term therapy with imatinib compared with the general population. *Blood*. 2011;118(17):4554-60.
6. Vener C, Banzi R, Ambrogi F, Ferrero A, Saglio G, Pravettoni G, et al. First-line imatinib vs second- and third-generation TKIs for chronic-phase CML: a systematic review and meta-analysis. *Blood Adv*. 2020 Jun 23;4(12):2723-735.
7. Wang Z, Wang X, Wang Z, Feng Y, Jia Y, Jiang L, et al. Comparison of hepatotoxicity associated with new bcr-abl tyrosine kinase inhibitors vs imatinib among patients with chronic myeloid leukemia: A systematic review and meta-analysis. *JAMA Netw Open*. 2021 ;4(7):e2120165.
8. Lin Q, Mao L, Shao L, Zhu L, Han Q, Zhu H, et al. Global, regional, and national burden of chronic myeloid leukemia, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Front Oncol*. 2020;10:580759.
9. Winn AN, Atallah E, Cortes J, Deininger MWN, Kota V, Larson RA, et al. Estimated savings after stopping tyrosine kinase inhibitor treatment among patients with chronic myeloid leukemia. *JAMA Netw Open*. 2023; 6(12):e2347950.
10. 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; 34:966–984.
11. 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(3):298-305.
12. Ross DM, Branford S, Seymour JF, Schwarzer 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(4):515-22.
13. Saussele S, Richter J, Guilhot J, Gruber FX, Hjorth-Hansen H, Almeida A, et al. EURO-SKI investigators. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*. 2018;19(6):747-57.

14. Kumagai T, Nakaseko C, Nishiwaki K, Yoshida C, Ohashi K, Takezako N, et al. Dasatinib cessation after deep molecular response exceeding 2 years and natural killer cell transition during dasatinib consolidation. *Cancer Sci*. 2018;**109**(1):182-92.
15. Takahashi N, Nishiwaki K, Nakaseko C, Aotsuka N, Sano K, Ohwada C, et al. Treatment-free remission after two-year consolidation therapy with nilotinib in patients with chronic myeloid leukemia: STAT2 trial in Japan. *Haematologica*. 2018;**103**(11):1835-42.
16. Fujisawa S, Ueda Y, Usuki K, Kobayashi H, Kondo E, Doki N, et al. Feasibility of the imatinib stop study in the Japanese clinical setting: delightedly overcome CML expert stop TKI trial (DOMEST Trial). *Int J Clin Oncol*. 2019;**24**(4):445-53.
17. Mahon FX, Boquimpani C, Kim DW, Benyamini N, Clementino NCD, Shuvaev V, et al. Treatment-free remission after second-line nilotinib treatment in patients with chronic myeloid leukemia in chronic phase: results from a single-group, phase 2, open-label study. *Ann Intern Med*. 2018;**168**(7):461-70.
18. Hochhaus A, Masszi T, Giles FJ, Radich JP, Ross DM, Gómez Casares MT, et al. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. *Leukemia*. 2017;**31**(7):1525-31.
19. Rea D, Nicolini FE, Tulliez M, Guilhot F, Guilhot J, Guerçi-Bresler A, et al. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. *Blood*. 2017;**129**(7):846-54.
20. Perusini MA, Novitzky-Basso I, Atenafu EG, Forrest D, Bence-Bruckler I, Savoie L, et al. Final report of TKI discontinuation trial with dasatinib for the second attempt of treatment-free remission after failing the first attempt with imatinib: Treatment-free Remission Accomplished by Dasatinib (TRAD) study. *Br J Haematol*. 2023;**203**(5):781-91.
21. Imagawa J, Tanaka H, Okada M, Nakamae H, Hino M, Murai K, et al. Discontinuation of dasatinib in patients with chronic myeloid leukaemia who have maintained deep molecular response for longer than 1 year (DADI trial): a multicentre phase 2 trial. *Lancet Haematol*. 2015;**2**(12):e528-35.
22. Shah NP, García-Gutiérrez V, Jiménez-Velasco A, Larson SM, Saussele S, Rea D, et al. Treatment-free remission after dasatinib in patients with chronic myeloid leukemia in chronic phase with deep molecular response: Final 5-year analysis of DASFREE. *Br J Haematol*. 2023;**202**(5):942-52.

23. Gottschalk A., Glauche I., Cicconi S., Clark R.E., Roeder I. Molecular monitoring during dose reduction predicts recurrence after TKI cessation in CML. *Blood*. 2020;135:766-69.
24. Dengler J, Tesch H, Jentsch-Ullrich K, Gerhardt A, Schulte C, Lipke J, et al. treatment-free remission in real-world chronic myeloid leukemia patients: Insights from German hematology practices. *Acta Haematol*. 2022;145(6):603-10.
25. Hernández-Boluda JC, Pereira A, Pastor-Galán I, Alvarez-Larrán A, Savchuk A, Puerta JM, et al. Feasibility of treatment discontinuation in chronic myeloid leukemia in clinical practice: results from a nationwide series of 236 patients. *Blood Cancer J*. 2018;**8**(10):91.
26. Benjamini O, Kantarjian H, Rios MB, Jabbour E, O'Brien S, Jain P, et al. Patient-driven discontinuation of tyrosine kinase inhibitors: single institution experience. *Leuk. Lymphoma*. 2014;**55**:2879-86.
27. Lurlo A, Cattaneo D, Artuso S, Consonni D, Abruzzese E, Binotto G, et al. Treatment-free remission in chronic myeloid leukemia patients treated with low-dose TKIs: a feasible option also in the real-life. A Campus CML Study. *Front Oncol*. 2022;12:839915.
28. Ferrero D, Cerrano M, Crisà E, Aguzzi C, Gai V, Boccadoro M. How many patients can proceed from chronic myeloid leukaemia diagnosis to deep molecular response and long-lasting imatinib discontinuation? A real life experience. *Br. J. Haematol*. 2017;**176**:669-671.
29. Ilander M, Olsson-Strömberg U, Schlums H, Guilhot J, Brück O, Lähdenmäki H. Increased proportion of mature NK cells is associated with successful imatinib discontinuation in chronic myeloid leukemia. *Leukemia*. 2017;31(5):1108-16.
30. Kumagai T, Nakaseko C, Nishiwaki K, Yoshida C, Ohashi K, Takezako N; Kanto CML, Shimousa Hematology Study Groups. Silent NK/T cell reactions to dasatinib during sustained deep molecular response before cessation are associated with longer treatment-free remission (D-STOP). *Cancer Sci*. 2020 ;111(8):2923-34.
31. Marcé S, Méndez A, Xicoy B, Estrada N, Cabezón M, Sturla AL, et al; Grupo Español de Leucemia Mieloide Crónica (GELMC). e14a2 transcript favors treatment-free remission in chronic myeloid leukemia when associated with longer treatment with tyrosine kinase inhibitors and sustained deep molecular response. *J Clin Med*. 2024;13(3):779.
32. Haddad FG, Sasaki K, Issa GC, Garcia-Manero G, Ravandi F, Kadia T, et al. Treatment-free remission in patients with chronic myeloid leukemia following the discontinuation of tyrosine kinase inhibitors. *Am J Hematol*. 2022;97(7):856-64.

33. Kim J, Park J, Moon Y, Choi SJ, Lim JH, Lee MH, et al. Effect of study-level factors on treatment-free remission rate in patients with chronic myeloid leukemia: a systematic review and meta-analysis. *Int J Hematol*. 2019;110(6):683-89.
34. Radich JP, Hochhaus A, Masszi T, Hellmann A, Stentoft J, Casares MTG, et al. Treatment-free remission following frontline nilotinib in patients with chronic phase chronic myeloid leukemia: 5-year update of the ENESTfreedom trial. *Leukemia*. 2021;35(5):1344-55.
35. Hughes TP, Clementino NCD, Fominykh M, Lipton JH, Turkina AG, Moiraghi EB, et al. Long-term treatment-free remission in patients with chronic myeloid leukemia after second-line nilotinib: ENESTop 5-year update. *Leukemia*. 2021;35(6):1631-42.
36. Shah NP, Bhatia R, Altman JK, Amaya M, Begna KH, Berman E, et al. Chronic Myeloid Leukemia, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2024;22(1):43-69.
37. Cheng F, Yuan G, Li Q, Cui Z, Li W. Long-term outcomes of frontline imatinib therapy for chronic myeloid leukemia in China. *Front Oncol*. 2023;13:1172910.
38. Rousselot P, Loiseau C, Delord M, Cayuela JM, Spentchian M. Late molecular recurrences in patients with chronic myeloid leukemia experiencing treatment-free remission. *Blood Adv*. 2020;4(13):3034-3040.
39. Rousselot P, Charbonnier A, Cony-Makhoul P, Agape P, Nicolini FE, Varet B, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. *J Clin Oncol*. 2014;32(5):424-30.
40. Geelen IGP, Thielen N, Janssen JJWM, Hoogendoorn M, Roosma TJA, Willemsen SP, et al. Treatment outcome in a population-based, 'real-world' cohort of patients with chronic myeloid leukemia. *Haematologica*. 2017;102(11):1842-49.

Table and figure legends:

Table 1. Baseline demographics and clinical characteristics of CML patients who discontinued TKI therapy

Table 2. Characteristics of the CML patients who relapsed after TKI discontinuation

Table 3. Risk Factors of Relapse after TKI Discontinuation

Figure 1. Treatment free remission of the 55 CML patients who discontinued TKI therapy

Table 1. Baseline demographics and clinical characteristics of CML patients who discontinued TKI therapy

Parameter	Values (n=55)
Female/Male	35/20
Age (years) at CML diagnosis, median (range)	40 (16-74)
Age at TKI stop, median (range)	48 (21-80)
Sokal score, n (%)	
Low	15 (27.3)
Intermediate	30 (54.5)
High	9 (16.4)
Not known	1 (1.8)
First-line TKI, n (%)	
Imatinib	48 (87)
Dasatinib	4 (7)
Nilotinib	3 (6)
Second-line TKI, n (%)	
None	29 (52.7)
Nilotinib	12 (22)
Dasatinib	8 (31)
Imatinib	6 (11)
Last TKI before discontinuation, n (%)	
Imatinib	29 (52.7)
Nilotinib	14 (25.45)

Dasatinib	12 (21.8)
Time (months) to achieve initial MMR, median (IQR)	12 (3;24)
Total duration of TKI therapy (months), median (IQR)	86 (60;132)
Duration of sustained DMR before TKI discontinuation, median (IQR)	66 (47;114)
Molecular response at discontinuation of TKI, n (%)	
CMR	55 (100)
Follow up after TKI discontinuation (months), median (IQR)	34 (12;68)

TKI: tyrosine kinase inhibitor; MMR: major molecular response; DMR: deep molecular response; CMR: complete molecular response; IQR: interquartile range

Table 2. Characteristics of the CML patients who relapsed after TKI discontinuation

Parameter	Values
Number of patients relapsed, n (%)	15 (27.3)
Median age (years) at relapse (range)	49 (21-70)
Gender: Female/Male	8/7
Sokal score	
High	2
Intermediate	11
Low	2
Total duration (months) of TKI therapy, median (range)	100 (52-182)
Last TKI at discontinuation	
Imatinib	11
Dasatinib	2
Nilotinib	2
Time (months) to relapse, median (range)	5 (3 – 38)
Time periods of relapse (n = 15)	
0-6 months	12 (80%)
6-12 months	2 (13.3%)
More than 12 months	1 (6.7%)
Time (months) to achieve MMR after re-initiation	3 (2 – 6)

of TKI, median (range)	
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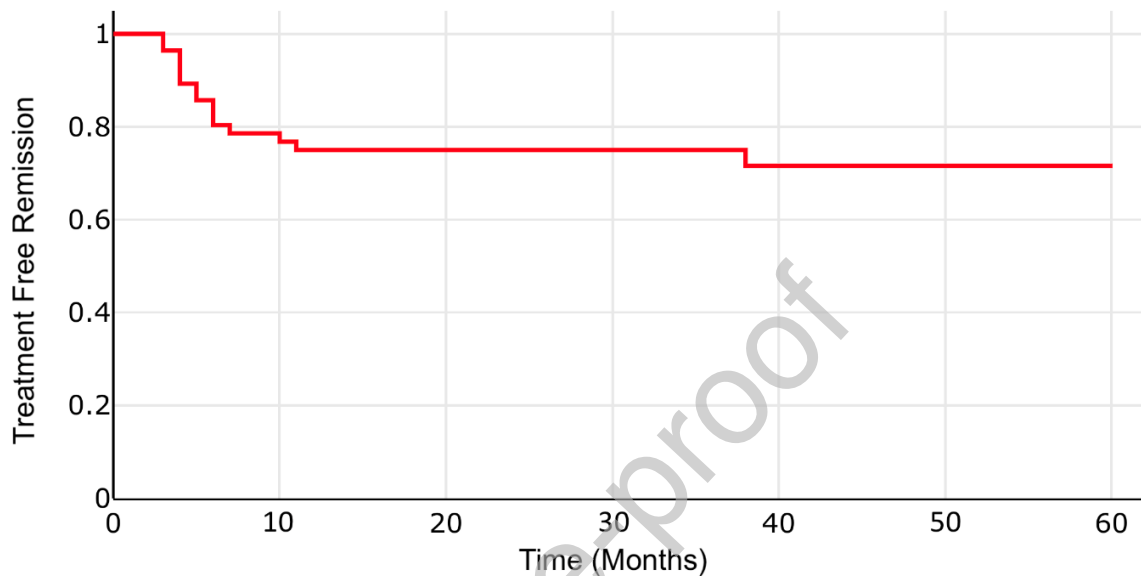
Table 3: Risk Factors of Relapse after TKI Discontinuation

Parameter	Unadjusted Odds Ratio	95% Confidence Interval (lower limit- upper limit)	p-value
Age at diagnosis (≤40 years vs >40 years)	1.48	0.45 – 4.89	0.521
Gender (Male vs female))	0.51	0.15 – 1.72	0.276
Sokal Score (low vs intermediate + high)	3.25	0.64 – 16.60	0.238
Time to achieve MMR (≤12 months vs >12 months)	1.55	0.45 – 5.25	0.483
Total duration of TKI treatment till discontinuation (86 months or less)	1.20	0.37 – 3.97	0.761
Duration of DMR (≥ 60 months vs < 60 months)	1.5	0.4 – 5.4	0.494

Probabilistic model is based on probability of having the relapse

MMR: major molecular response; DMR: deep molecular response

Figure 1. Treatment free remission of the 55 CML patients who discontinued TKI therapy



Clinical Practice points:

- What is already known about this subject?** Discontinuation of tyrosine kinase inhibitors (TKI) and treatment free remission (TFR) has shown to be safe and feasible in clinical studies and can be achieved in 40% to 60% of CML patients. Less is known about the safety and feasibility of this approach in the real-world practice, particularly from limited-resource countries.
- What are the new findings?** This real-world retrospective study found that discontinuation of TKI therapy and TFR is safe and feasible in routine clinical practice and can be achieved in around 72% of chronic-phase CML patients. Although not supported by statistical significance, most of the patients in this study received long TKI

therapy after deep remission (all patients had achieved complete molecular response), usually more than 5 years. Majority of the patients (87.3%) received imatinib as the first line treatment and slightly more than half of patients were receiving imatinib at the time of TKI discontinuation.

- **How might it impact on routine clinical practice?** Our study provides further reassurance to the physicians treating CML that discontinuation of TKI therapy is safe and feasible in routine clinical practice and TFR can be achieved in more than two-third of patients who achieved deep remission and received longer TKI therapy. Generic imatinib is cheaper and a number of CML patients receiving imatinib can expect to discontinue therapy making this approach feasible and practical in many resource-constrained countries.

Microabstract:

Discontinuation of TKI therapy and treatment free remission (TFR) was evaluated in chronic-phase CML patients in a real-world practice. This study showed that discontinuation of TKI therapy was safe and feasible in routine clinical practice and successful TFR was achieved in more than two-thirds of carefully selected patients with longer duration of TKI therapy after attaining deep molecular remission.