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Review Article

Redefining treatment-free remission criteria in chronic myeloid leukemia in India

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ABSTRACT

Chronic myeloid leukemia (CML) is the most common hematological malignancy in India and its treatment has been revolutionized by BCR-ABL tyrosine kinase inhibitors. Even though it is considered non-curable, with long-term treatment, a selected set of patients may be eligible for stoppage of treatment and continued observation (treatment-free remission [TFR]) according to the current guidelines. All these guidelines are from other countries and at present, Indian oncologists and patients have to follow these guidelines to implement TFR protocols.

The commonly used international guidelines also have differences in the methods of implementation of TFR in CML. There are very few articles from India with data on TFR in CML and we need to gather more data if we are to formulate our own criteria and guidelines.

Indian patients have a unique set of problems with the disease biology and its treatment. The potential issues with implementing TFR among Indian patients have to be identified and solved successfully and these have to be taken into account before creating such criteria for India.

The review aims to summarize the current criteria in place for TFR in CML, to discuss the issues in implementing the criteria directly in India, to define the needs of India CML patients, and to recommend the considerations to be taken into account while redefining such a criteria for Indian patients.

Keywords: Chronic myeloid leukemia, Criteria, India, Redefine, Treatment-free remission

INTRODUCTION

Chronic myeloid leukemia (CML) is one of the most common adult leukemias in the Indian population accounting for 30–60% of all adult leukemias.[1] There is a significant age difference in the Indian population as compared to the Western world, mean age at diagnosis being lesser by 10 years in Indians as compared to the Western world in most studies.[2] The landscape of CML has undergone a dramatic change in India as in the Western world with the introduction of BCR-ABL tyrosine kinase inhibitors (TKIs). Now with the availability of good quality generics of first and second-generation TKIs, more and more CML patients in India are having long-term control of the disease.

TREATMENT-FREE REMISSION (TFR) AND ITS IMPLICATIONS

Over 20 years of experience in using TKIs in CML has led us to better understanding of disease control and that there is at least a subset of patients in whom TKIs can be safely stopped if the disease activity can be strictly monitored. The concept of TFR has now been generally accepted

as safe and achievable, especially in patients on treatment for a long time. With close monitoring and follow-up, various studies have shown that about 40–60% of patients can be kept off treatment in the long term.[3] Even if treatment failure occurs (loss of molecular response), studies have shown that the TKI discontinuation has no impact on clinical outcomes.[4]

There are multiple international guidelines that have endorsed treatment-free remission with strict criteria for monitoring and restarting treatment [Table 1].

National Comprehensive Cancer Network (NCCN) guidelines for TKI discontinuation recommend that TKI may be stopped if,

- Age ≥18 years
- Chronic phase-CML. No prior history of accelerated phase-CML or blastic phase-CML
- On approved TKI therapy for at least 3 years
- Prior evidence of quantifiable BCR-ABL1 transcript
- Stable molecular response (MR4; BCR-ABL1 ≤0.01% International scale [IS]) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart
- Access to a reliable polymerase chain reaction (PCR) test with a sensitivity of detection of at least MR4.5 (BCR-ABL1 ≤0.0032% IS) and that provides results within 2 weeks
- Molecular monitoring every 1–2 months for the first 6 months following discontinuation, bimonthly during months 7–12, and quarterly thereafter (indefinitely) for patients who remain in major molecular response (MMR) (MR3; BCR: ABL1 ≤0.1% IS)
- Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. If MMR is not achieved after 3 months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months

The European Society of Medical Oncology guidelines[5] recommend that treatment discontinuation may be considered in individual patients, if proper, high-quality, and certified monitoring can be ensured. Prerequisites for safe stopping are institutional requirements for safe supervision, identification of typical BCR-ABL1 transcripts at diagnosis, at least 5 years of TKI therapy, achievement of MR4.5 (4.5-log reduction), and a stability of deep molecular response (DMR) (at least MR4) for at least 2 years. Less stringent criteria do not exclude successful TFR, but the stability of TFR is improved with longer TKI therapy and longer DMR. Informed consent should include information on the estimated risk of recurrence of the disease and the need for frequent molecular monitoring, monthly during the first half-year, 6-weekly during the second half-year, and 3-monthly later on life long.

TKI WITHDRAWAL SYNDROME ADDED TOXICITY OF DRUG WITHDRAWAL

TKI withdrawal syndrome is defined as the onset of new musculoskeletal pain and/or an increase in pre-existing pain and/or the need to start any pain medication. It usually occurs a few weeks after TKI discontinuation and is characterized by musculoskeletal pain and occurs in around 30% patients on stopping TKIs. There may be a need for the use of paracetamol, non-steroidal anti-inflammatory drugs,and steroids in severe cases. It is not dependent on prior TKI use.[6] The positive side of this is that the patients who have TKI withdrawal syndrome have a greater chance of TFR.[7] Patients with older age, longer TKI use, low body mass index, and body weight also have greater chances of withdrawal syndrome.[8] The implication of this among Indian patients is that patients who are typically leaner and on TKI for longer time, especially elderly, should be warned about the TKI withdrawal symptoms and necessary remedies for the same, as many patients in rural India may find it difficult to reach their treatment centers if they develop symptoms.

PSYCHOLOGICAL IMPLICATIONS OF TKI DISCONTINUATION

Patients may experience anxiety as a result of fluctuating BCR-ABL results during TFR. This has to be weighed against the mental fatigue and boredom of continuing TKI daily and lifelong. Hence, they should be adequately counseled and highly motivated for the same. They may have a fear of disease recurrence and progression, especially as they have been living with a well-controlled disease for a long time to be eligible for discontinuation. Hence, psychological and emotional factors from patient and physician perspectives have to be addressed in each visit in the long-term decision-making.

TREATMENT-FREE REMISSION - THE INDIAN EXPERIENCE

There are few published studies on the experience of TFR from India. The studies by Sarma *et al.*[9] and by Sarma *et al.*[10] from Tata Memorial Hospital, Mumbai are both retrospective analyses including a total of 66 patients. They report a long-term TFR of 70–80% in these studies. The prospective study by Goni *et al.*[11] included 26 patients on generic imatinib. They reported a TFR rate of 44% at 1 year among the patients included. A retrospective study on pediatric CML patients by Satishkumar *et al.*[12] reports a TFR of 72% among the 18 patients included. The small number of patients and retrospective nature of most of these studies precludes deriving conclusions and data for Indian patients as a whole and points to the need for large, well-designed prospective

Table 1: Comparison of various guidelines.

	Leukemia and Lymphoma NET	Leukemia NET	NCCN	ESMO
Diagnostic phase	Chronic (Mandatory)	Chronic (Mandatory)	Chronic phase	Chronic phase
Type of transcript	B3a2 (e14a2), or b2a2 (e13a2), typical isoform of 210 mandatory	Typical e13a2 or e14a2 BCR-ABL transcripts minimal	Quantifiable BCR-ABL transcript	Typical b2a2-or b3a2-BCR-ABL transcripts or atypical transcripts that can be quantified over a 4.5 log range
Sokal risk	High-risk warning	Not mentioned	Not mentioned	Non-high risk
Failure	Second line due to intolerance	No failure to first line	Not mentioned	No failure to first line
TKI treatment	>5 years for all TKI	>4 years 2nd G TKI >5 years 1st G TKI	>3 years	>5 years
Depth of MR required	MR 4.5 mandatory	MR 4.0 (>3 years) minimal MR 4.5 (>2 years)	MR 4.0	MR 4.5
Duration of DMR	>2 years mandatory	>2 years if MR 4.0 minimal >3 years if MR 4.0 OPTIMAL >2 years if MR 4.5 optimal	>2-year MR 4.0	>2-year MR 4.0–MR 4.5
Monitoring during TFR phase	Month 1–6 monthly Month 6–12 every 2–3 m Every 3 m thereafter	Month 1–6 monthly Month 6–12 every 2 m Every 3 m thereafter	Month 1–6 monthly Month 6–12 every 2 m Every 3 m thereafter	Month 1–6 monthly Month 6–12 every 6 weeks Every 3 m thereafter
TKI reinitiation	Loss of MMR	Loss of MMR	Loss of MMR	
Other aspects	Results within 2–3 weeks Psychosocial considerations Pharmaco-economic aspects Withdrawal syndrome management	Rapid turnaround results motivated patient with structured communication mandatory Patients agree to more frequent monitoring after stopping TKI. Mandatory	Results within 2 weeks No history AP-BC	Rapid turnaround results within 4 weeks institutional

NCCN: National Comprehensive Cancer Network guidelines, ESMO: European Society of Medical Oncology, G: Generation, MR: Molecular response as log reduction, CP: Chronic phase, AP: Accelerated phase, BC: Blast crisis, MMR: Major molecular response, IS: International scale, TKI: Tyrosine kinase inhibitor, TFR: Treatment-free remission, DMR: Deep molecular response, BCR-ABL: Breakpoint cluster region -Abelson, NET: Network

studies among Indian patients for deriving conclusions on the effect of TFR among Indian CML patients.

THE IMPLICATIONS OF TREATMENT-FREE REMISSION AMONG INDIAN PATIENTS

Treatment-free remission is a difficult challenge to deal with in India, especially rural India due to the stringent guidelines in place for discontinuation. It requires close monitoring, highly standardized tests, and dedicated and close follow-up, with high diligence and effort from both the patient and the treating oncologist.

There is an urgent need for identifying and initiating patients on TFR protocol in India because

a. Younger age at diagnosis means that the patients will be on treatment for a longer time - hence more benefit may be derived from TFR in Indian patients
b. Younger age patients being higher in number means that higher number of patients may be of childbearing age and may require TKI discontinuation to complete their families
c. Long-term adherence of Indian patients to TKIs is poor.[13] Most Indian studies[14] show that up to 1/3rd patients have poor adherence to treatment. If treatment can be discontinued safely, it may be beneficial overall

On the other hand, direct application of guidelines from the Western world to our setting has significant limitations because

a. Higher number of patients with Imatinib resistance mutations - with up to 45–50% resistance mutations identified in patients with poor response to Imatinib in some Indian studies[15,16]
b. The cost of treatment versus cost of testing - the usual cost of testing with quantitative PCR with the specificity

requirement as per guidelines will be equivalent to the cost of 2–3 months of treatment with generic Imatinib at the time of writing this article in India. Hence, in a financial sense, it might be more acceptable for economically challenged patients to just continue the drug

c. Added cost of travel and frequent visits to tertiary care cancer centers for testing, results, and increased number of consultations
d. Lack of access to standardized laboratories as per the strict guidelines - most laboratories do not offer tests at the specificity of MR4.5 levels. This means that only patients who have access to the selected laboratories will be able to stop the TKIs safely
e. Low turnaround time (as per NCCN guidelines) - considering the time taken for the transport of specimens to laboratories with high accuracy testing and number of specimens needed for economically viable testing means that the guideline for turnaround time is impractical for a country like India.

The need to redefine treatment-free remission criteria in Indian CML patients and considerations to be taken into account for Indian patients.

As discussed above, the direct application of guidelines from other countries may not be feasible in India and if we try to do so, the option of TFR may be accessible only to a very limited number of patients. However, the lack of data and standardization of laboratories and lack of motivation for TKI discontinuation among both the patients and physicians restrict us from taking action in this regard. The burden of CML treatment can be significantly reduced if treatment-free remission criteria are redefined for Indian patients and the considerations to be taken into account while designing such as criteria should be

- Uniform standardization of laboratories as per Indian laboratory standardization protocols which most Indian laboratories adhere to for accreditation
- The criteria of molecular response should be made less sensitive so that testing can be done in more laboratories and at lower cost. The current evidence points to the fact that almost all patients re-achieve molecular remission on restarting TKI, so it may be time to relax the criteria if it benefits more patients
- The turnaround time mentioned in some criteria must also be relaxed if a significant number of Indian patients are to benefit from TFR
- Strict criteria for defining TKI withdrawal syndrome and guidelines for its management should be included
- The frequency of testing should be reduced at least after the initial phase of high risk of treatment failure so that the patient is not simply exchanging the burden of taking TKI for their lifetime for the burden of a lifetime of frequent hospital visits and costly testing.

The redefinition of the treatment-free remission criteria for CML should be done at the earliest with the involvement of a regulatory body of national experts so that Indian CML patients will also get the benefit of TFR with a set of guidelines feasible for India without compromising on disease control.

CONCLUSION

The common International guidelines of stopping TKIs for CML may not be practical in India due to multiple factors. Taking the unique biological, clinical and social scenario of India into account, it may be time for India to redefine and formulate its own guidelines for TKI stoppage in Indian CML patients.

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REFERENCES

1. Bansal S, Prabhash K, Parikh P. Chronic myeloid leukemia data from India. Indian J Med Paediatr Oncol 2013;34:154-8.
2. Bhutani M, Pathak AK, Sengar M, Gupta SD, Jain P, Thulkar S, *et al*. Multifocal osteosarcoma involving unusual sites. Cancer Invest 2006;24:278-82.
3. Saifullah HH, Lucas CM. Treatment-free remission in chronic myeloid leukemia: Can we identify prognostic factors? Cancers (Basel) 2021;13:4175.
4. Chen KK, Du TF, Xiong PS, Fan GH, Yang W. Discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia with losing major molecular response as a definition for molecular relapse: A systematic review and meta-analysis. Front Oncol 2019;9:372.
5. Hochhaus A, Saussele S, Rosti G, Mahon FX, Janssen JJ, Hjorth-Hansen H, *et al*. Chronic myeloid leukemia: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv41-5.
6. Berger MG, Pereira B, Oris C, Saugues S, Cony-Makhoul P, Gardembas M, *et al*. Osteoarticular pain after discontinuation of tyrosine kinase inhibitors (TKI): A french cohort. Blood 2015;126:137.
7. Lee SE, Choi SY, Song HY, Kim SH, Choi MY, Park JS, *et al*. Imatinib withdrawal syndrome and longer duration of imatinib have a close association with a lower molecular relapse after treatment discontinuation: The KID study. Haematologica 2016;101:717-23.
8. Petrova A, Chelysheva E, Shukhov O, Bykova A, Nemchenko I, Gusarova G, *et al*. Withdrawal syndrome after tyrosine kinase

inhibitor discontinuation in patients with chronic myeloid leukemia in the Russian prospective study RU-SKI. Clin Lymphoma Myeloma Leuk 2020;20:267-71.
9. Sarma RJ, Kashyap L, Srikanth A, Mondal T, Kashyap Y, Nandhana R, *et al*. Real world outcomes with treatment free remission in chronic myeloid leukemia-experience from a tertiary care cancer centre. Indian J Hematol Blood Transfus. 2024;40:564-2.
10. Sarma R, Thorat J, Nayak L, Jain H, Sengar M, Banavali S, *et al*. CML-428 real world data of treatment free remission (TFR) in patients with chronic myeloid leukemia (CML) treated at a tertiary care oncology center in India. Clin Lymphoma Myeloma Leuk 2022;22:S298-9.
11. Goni D, Jain A, Singh C, Jindal N, Nampoothiri R, Jandial A, *et al*. Feasibility of treatment-free remission with generic imatinib: Results of generic imatinib-free trial-in-chronic myeloid leukemia-chronic phase study. Indian J Med Res 2023;157:87-91.
12. Satishkumar M, Venkateswaran VS, Kavitha G, Suresh D, Sohini C, Ramya U, *et al*. Treatment free remission in pediatric chronic myeloid leukemia. Pediatr Hematol Oncol J 2023;8: 27-30.
13. Menon H. Non-adherence to CML therapy and its clinical implications in India. Natl Med J India 2017;30:142-7.
14. Ganesan P, Sagar TG, Dubashi B, Rajendranath R, Kannan K, Cyriac S, *et al*. Nonadherence to imatinib adversely affects event free survival in chronic phase chronic myeloid leukemia. Am J Hematol 2011;86:471-4.
15. Sharma P, Mohanty S, Kochupillai V, Kumar L. Mutations in ABL kinase domain are associated with inferior progression-free survival. Leuk Lymphoma 2010;51:1072-8.
16. Kagita S, Uppalapati S, Jiwatani S, Linga VG, Gundeti S, Nagesh N, *et al*. Incidence of Bcr-Abl kinase domain mutations in imatinib refractory chronic myeloid leukemia patients from South India. Tumour Biol 2014;35:7187-93.

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