Abstract : Both innovator and generic imatinib are approved for the treatment of Chronic Myeloid Leukemia-Chronic phase (CML-CP). Currently, there are no studies on the feasibility of treatment free remission (TFR) with generic imatinib. In a single center prospective Generic Imatinib Free Trial - in -CML-CP (GIFT-in-CML-CP) study, twenty-six patients on generic imatinib for 3 years and in sustained deep molecular response (BCR ABL^{IS} <0.01% for more than 2 years) were included. After treatment discontinuation, patients were monitored with complete blood count and BCR ABL^{IS} by real time quantitative PCR monthly for one year and three monthly thereafter. Generic imatinib was restarted at single documented loss of major molecular response. At a median follow-up of 20 months (range, 4-34 months), 42.3% patients (n=11) continued to be in TFR. Estimated TFR at 1 year was 44%. All patients restarted on generic imatinib regained major molecular response. On multivariate analysis, attainment of complete molecular remission (CMR) prior to TFR trial was predictive of TFR [p=0.022, HR 0.284 (0.096-0.837)]. We conclude that , generic imatinib can be safely discontinued in CML-CP patients who are in deep molecular remission.

Main Manuscript

Introduction

Chronic Myeloid Leukemia (CML) is curable with the use of tyrosine kinase inhibitors (TKI).[1] IRIS trial reported overall survival of 83.3% at 10 years with imatinib mesylate in patients with CML. [2,3] Generic imatinib for the treatment of CML has been available since 2002 in India, 2012 in Europe, 2015 in Canada and 2016 in USA.[4–6] Efficacy of generic imatinib has remained controversial because of lack of large comparative studies with innovator molecule.[7–9] Despite that, generic imatinib is widely used because of its lower financial burden, and consequently improved adherence to TKI.[10,11]

Lifelong treatment with TKI has a significant impact on quality of life (QoL).[12] Therefore, treatment free remission (TFR) has emerged as an important goal in the management of CML. It has evolved from clinical trials to routine healthcare practice. Multiple trials have shown that TFR can be achieved in nearly 40% of patients who are in sustained deep molecular response, after discontinuation of the first-line therapy.[13] Similar data on achievement of TFR with generic imatinib are lacking. Therefore, in a prospective study we addressed this question of feasibility of TFR with generic imatinib.

Materials and methods

This single centre prospective trial **Generic Imatinib Free Trial -in-CML-CP(GIFT-in-CML-CP)** was conducted at a tertiary care centre in India from January 2017 to December 2019. CML-CP patients, aged more than 18 years on generic imatinib (Veenat, beta crystalline form, Natco pharmaceuticals, Hyderabad India) for more than 3 years with sustained Deep Molecular Response for more than 2 years were eligible for the study. Deep Molecular Response (DMR) was defined as BCR ABL^{IS} <0.01% i.e. MR >4. Complete Molecular response (CMR) was defined as undetectable BCR ABL level (PCR detection limit BCR ABL^{IS} >0.001%). Diagnosis of CML was based on bone marrow examination and demonstration of Philadelphia chromosome on karyotype or detection of BCR ABL transcript by RT PCR. An informed consent was obtained from all patients and the study protocol was approved by the Institute Ethics Committee. The trial was registered under clinical trial registry, India (CTRI/2018/08/015357).

After treatment discontinuation patients were followed up with complete blood count and RQ-PCR for BCR-ABL^{IS} monthly for the first one year and every 3 months thereafter . Loss of MMR at any single time point was the criteria for TFR failure and an indication to restart imatinib. To identify prognostic factors, all variables associated with the outcome at 0·20 level on univariate analysis were simultaneously entered into a Cox regression model. Significance was set at a p value of 0.05. Estimates for hazard ratios and corresponding 95% Confidence Intervals (CI) were obtained for significant outcome factors.

Results

From January 2017 to November 2019, twenty-six patients (male: 14, female: 12) with median age 57 years (range, 32-73 years) were enrolled. Baseline Sokal score was low in 16 (61.5%), intermediate in 8 (30.7%) and high in 2 (7.7%). The median duration of treatment with generic imatinib was 6.9 years (range, 3.1-15). At the time of treatment discontinuation, 18 patients had CMR (69.2%) and 8 had DMR (30.8%). Prior to imatinib discontinuation, the median duration of DMR was 4.2 years (range, 2.1-10 years) (Table 1).

After a median follow-up of 20 months (range, 4-34), 11 of the 26 patients (42.3%) continued to be in TFR while 15 patients (57.7%) had loss of MMR. The median time to loss of MMR was 3 months (range, 2-21 months). Twelve of the 15 patients (80%) had loss of MMR within 6 months of treatment discontinuation, the other three had loss of MMR at 9, 12 and 21 months respectively. By Kaplan-Meier analysis the estimated probability of remaining in TFR was 61% at 3 months, 53% at 6 months and 44% at 12 months (figure 1A).

Age, gender, baseline Sokal score, time to MMR, depth of molecular remission, duration of imatinib and duration of DMR were analysed as potentially predictive factors for TFR durability (Table 2). On univariate analysis, only depth of molecular response (CMR vs not in CMR) at the time of treatment discontinuation was found to be predictive of TFR durability (p=0.020) (figure 1B). An age cut off of 56.5 years also showed a trend towards statistical significance (p=0.137). On multivariate analysis using cox regression, only depth of molecular response remained significant (p=0.022) with HR 0.284 (0.096-0.837).

Three of the 26 patients (11.5%) developed TKI withdrawal syndrome after stopping imatinib. Two patients had fatigue and non-specific body aches after one month of imatinib discontinuation. One female patient developed bilateral lower limb pain with left

suprapatellar bursitis after 7 months of treatment discontinuation. She responded to anti-inflammatory agents and continues to be in TFR at 19 months follow up.

All 15 patients with loss of MMR were restarted on treatment with generic imatinib and attained MMR after a median duration of 1 month (range, 1-4 months). Thirteen of these 15 patients have a follow up of more than 12 months after commencing retreatment: 6 have regained CMR and 7 had regained DMR. There has been no loss of haematological response or disease progression in any of the patients.

Discussion Generic Imatinib has provided a cost effective alternative TKI option to large number of patients with CML.TFR with generic versions of imatinib has not been studied till date. Wide range of generic versions of imatinib (alpha, beta or gamma crystalline forms of imatinib mesylate) are available across different countries. [14–17] There are growing number of studies with different generic forms of imatinib with contradicting findings.While majority of studies have shown that generic and innovator imatinib are equally efficacious, [14] a few have suggested loss of responses when switched from innovator to generic version of imatinib [8]. Besides, certain studies have also suggested that medication persistence may be lower with generic imatinib, mainly driven by excessive adverse events as compared to innovator.[18] Persistence on a given TKI for more than 3 years and attainment of DMR both are pre-requisites for TFR trial, therefore a TFR study on generic imatinib potentially addressees both tolerability and efficacy controversies that surround generic imatinib use.

One year TFR rate of 44% with generic imatinib in the current study is similar to the previous studies with innovator imatinib [13,19] None of our patients had disease progression and all patients with TFR failure were able to re-attain MMR with generic imatinib. These findings support the efficacy and feasibility of TFR with generic imatinib.

While duration of TKI treatment and duration of deep molecular response are known prognostic factors for a durable TFR, they were not found to be prognostic in our cohort.[20] This may be explained by the relatively small number of patients who received imatinib for less than 4 years or had sustained DMR for less than 3 years in our cohort (4 and 6 patients respectively). In our cohort, only depth of molecular response (CMR vs not in CMR) at the time of treatment discontinuation was found to be predictive of TFR durability ($p=0.020$) (figure 1B). This finding however needs confirmation in a larger cohort.

The incidence of transient TKI withdrawal syndrome in the form of mild musculoskeletal symptoms was found to be 30% in previous studies with innovator imatinib.[21] The KIDS study from Korea demonstrated that occurrence of TKI withdrawal syndrome was associated with lower risk of molecular relapse[22] In our study 3 patients (11.5%) developed TKI withdrawal and one of them continues to be in TFR at 19 months follow up.

As this study included patients taking a single generic imatinib version, findings may not be generalizable to other generic versions of imatinib. Limited patient number, lack of comparator arm with innovator molecule and short duration of follow up are the other limitations of the study.

Conclusion

This study showed similar rates of TFR with generic imatinib. The findings of this study should instill confidence in the minds of CML patients and physicians regarding the safety as well as efficacy of generic imatinib in achieving TFR. Fututre TFR studies using different formulations of generic imatinib and comparator arms

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Data Availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest :None

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References

1. Yanamandra U, Malhotra P. CML in India: Are We There Yet? Indian J Hematol Blood Transfus. 2019;35(1):1–2.
2. Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. N Engl J Med. 2017;376(10):917–27.
3. Deininger M, O'Brien SG, Guilhot F, Goldman JM, Hochhaus A, Hughes TP, et al. International Randomized Study of Interferon Vs STI571 (IRIS) 8-Year Follow up: Sustained Survival and Low Risk for Progression or Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with

Imatinib. Blood. 2009;114(22):1126–1126.

4. Experts in Chronic Myeloid Leukemia E in CM, Abboud C, Berman E, Cohen A, Cortes J, DeAngelo D, et al. 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;121(22):4439–42.
5. Conti RM, Padula W V, Larson RA. Changing the cost of care for chronic myeloid leukemia: the availability of generic imatinib in the USA and the EU. Ann Hematol. 2015;94(2):249–57.
6. Chen CT, Kesselheim AS. Journey of Generic Imatinib: A Case Study in Oncology Drug Pricing. J Oncol Pract. 2017;13(6):352–5.
7. Eskazan AE, Ar MC, Soysal T. The efficacy and tolerability issue of generics of imatinib in the treatment of chronic myeloid leukemia: do generics really jeopardize patient safety? Leuk Lymphoma. 2015;56(4):1182–3.
8. Saavedra D, Vizcarra F. Deleterious effects of non-branded versions of imatinib used for the treatment of patients with chronic myeloid leukemia in chronic phase: a case series on an escalating issue impacting patient safety. Leuk Lymphoma. 2014;55(12):2813–6.
9. Alwan AF, Matti BF, Naji AS, Muhammed AH, Abdulsahib MA. Prospective single-center study of chronic myeloid leukemia in chronic phase: switching from branded imatinib to a copy drug and back. Leuk Lymphoma. 2014;55(12):2830–4.
10. Mathews V. Generic imatinib: the real-deal or just a deal? Leuk Lymphoma. 2014;55(12):2678–80.
11. Campbell D, Blazer M, Bloudek L, Brokars J, Makenbaeva D. Realized and Projected Cost-Savings from the Introduction of Generic Imatinib Through Formulary Management in Patients with Chronic Myelogenous Leukemia. Am Heal Drug Benefits. 2019;12(7):333.
12. Yanamandra U, Malhotra P, Sahu KK, Sushma Y, Saini N, Chauhan P, et al. Variation in Adherence Measures to Imatinib Therapy. J Glob Oncol. 2018;(4):1–10.
13. 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.
14. Ćojbašić I, Mačukanović-Golubović L, Vučić M, Ćojbašić Ž. Generic Imatinib in Chronic Myeloid Leukemia Treatment: Long-Term Follow-up. Clin Lymphoma Myeloma Leuk. 2019;19(9):e526–31.
15. Abou Dalle I, Kantarjian H, Burger J, Estrov Z, Ohanian M, Verstovsek S, et al. Efficacy and safety of generic imatinib after switching from original imatinib in patients treated for chronic myeloid leukemia in the United States. Cancer Med. 2019;8(15):6559–65.
16. Danthala M, Gundeti S, Kuruva SP, Puligundla KC, Adusumilli P, Karnam AP, et al. Generic Imatinib in Chronic Myeloid Leukemia: Survival of the Cheapest. Clin Lymphoma Myeloma Leuk. 2017;17(7):457–62.
17. de Lemos ML, Kyritsis V. Clinical efficacy of generic imatinib. J Oncol Pharm Pract. 2015;21(1):76–9.
18. Klil-Drori AJ, Yin H, Azoulay L, Harnois M, Gratton M-O, Busque L, et al. Persistence with generic imatinib for chronic myeloid leukemia: a matched cohort

study. Haematologica. 2019;104(7):e293 LP-e295.

19. Mahon F, Richter J, Guilhot J, Hjorth-Hansen H, Almeida A, Janssen JJWMJ, et al. Cessation of Tyrosine Kinase Inhibitors Treatment in Chronic Myeloid Leukemia Patients with Deep Molecular Response: Results of the Euro-Ski Trial. Blood. 2016;128(22).

20. Saußele S, Richter J, Hochhaus A, Mahon F-X. The concept of treatment-free remission in chronic myeloid leukemia. Leukemia. 2016;30(8):1638–47.

21. Hughes TP, Boquimpani C, Kim D-W, Benyamini N, Clementino NCD, Shuvaev V, et al. Treatment-free remission (TFR) in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) treated with second-line nilotinib (NIL): First results from the ENESTop study. J Clin Oncol. 2016;34(15_suppl):7054–7054.

22. Lee S-E, Choi SY, Song H-Y, Kim S-H, Choi M-Y, 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(6):717–23.

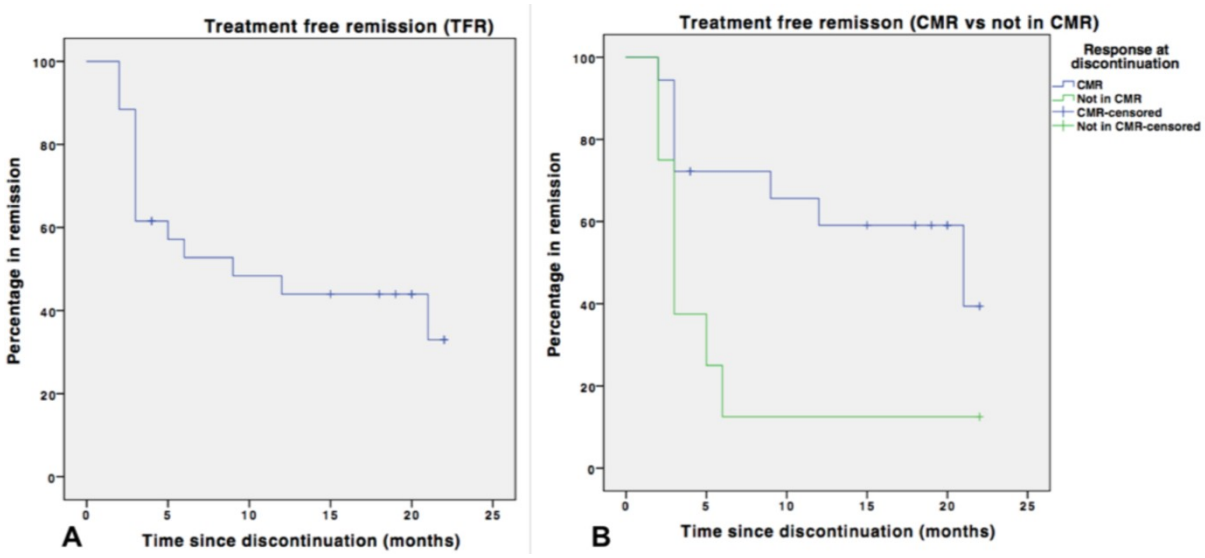

Figure legends

Figure 1. Kaplan Meier plots of major molecular remission free survival. (A) For the entire cohort. (B) By depth of molecular response at treatment discontinuation (CMR vs. not in CMR).

Table1 : Baseline Characteristics of study population

Characteristic	Data
Age, years Median (range)	 57 (32-73)
Gender (%) Male Female	 14 (54) 12 (46)
Sokal (%) Low Intermediate High	 16 (61.5) 8 (30.8) 2 (7.7)
Duration of imatinib prior to discontinuation, years Median (range)	 6.9 (3.1-15)
Depth of remission (%) CMR Not in CMR	 18 (69.2) 8 (30.8)
Duration of deep molecular remission, years Median (range)	 4.25 (2.1-10)

CMR: Complete Molecular Remission

Table 2 Potential factors for prediction of molecular relapse by univariate analysis

Potential predictive factor	Estimated survival without loss of MMR at 12 months, %	Median survival without loss of MMR, months (95% CI)	P Value
Age			0.137
≤ 56.5 years	57.7	21 (4-37.9)	
> 56.5 years	30.8	3 (0.8-5.1)	
Sex			0.697
Male	40.2	6 (0-12)	
Female	48.6	12 (0-35)	
Sokal			0.266
Low	53.5	21 (0-42)	
Intermediate or high	30	(1.1-4.8)	
Time to MMR			0.669
≤ 12 months	45.7	5 (0-15.6)	
> 12 months	20	6 (0-12)	
Depth of molecular response			0.020
CMR	59.1	21 (4.9-37)	
Not in CMR	12.5	3 (2.1-3.8)	
Duration of Imatinib			0.258
≤ 105 months	38.5	5 (0-15)	
> 105 months	62.5	Not reached	
Duration of DMR			0.942
≤ 40.5 months	50	5 (0-15)	
40.6 -78 months	45.7	6	
> 78 months	26.7	12 (4.5-19.4)	

CI: Confidence Interval, CMR: Complete Molecular Remission, DMR: Deep Molecular Response