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Chronic Myeloid Leukemia- The Promise of Tyrosine Kinase Inhibitor Discontinuation

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Abstract

Some believe that tyrosine kinase inhibitor (TKI) therapy is as close to perfect as it gets in oncologic therapy. Patients diagnosed with chronic myeloid leukemia (CML) are treated with a daily oral therapy, through which most achieve remission. TKI therapy is not associated with classic chemotherapy side effects, and most patients are able to resume their normal activities of daily living. Moreover, recent data has demonstrated that CML does not affect the life expectancy of patients whose disease is well-controlled with a TKI. However, TKI therapy is actually not that perfect. Patients need to stay on therapy forever. They have to remember to take their medications daily. TKIs are expensive, and the financial burden to patient and society cannot be overstated. Most patient's health-related quality of life is affected; common side effects include fatigue, muscle cramps, pain, edema, skin problems, and gastrointestinal symptoms. In addition, concerns about long-term side effects remain. Recently several studies have shown the feasibility and safety of discontinuation in a select group of patients. Herein, we will review the currently available data on stopping TKIs in CML.

Keywords

Chronic Myeloid Leukemia; Costs of therapy; Quality of life; Tyrosine kinase inhibitors
Discontinuation; Treatment Free Remission; TKI Stop studies

Introduction

Patients diagnosed with chronic myeloid leukemia (CML) are usually relieved to hear that treatment is with an oral therapy (not intravenous), is fairly well tolerated, and most patients

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Conflict of Interest

Ravi Kishore Narra and Kathryn E. Flynn each declare no potential conflicts of interest. Ehab Atallah reports personal fees from BMS, personal fees from Novartis, personal fees from Pfizer, and personal fees from Ariad outside the submitted work.

Human and Animal Rights and Informed Consent

This article contains no studies with human or animal subjects performed by any of the authors.

will respond to this therapy. However, the life-long duration of therapy with tyrosine kinase inhibitors (TKIs) is often a disappointment, which can be experienced either at the time of diagnosis or after many years when patients are tired of taking their pills. In addition, health-related quality of life is markedly affected in many patients. Several studies published since 2010 have demonstrated the safety and feasibility of discontinuing TKI therapy in patients who have achieved a sustained deep molecular response. In this paper, we review currently available data on the safety and efficacy of stopping TKIs, starting with reasons for discontinuation.

Why consider stopping?

Though the survival rates for patients treated with TKIs have tremendously improved compared to previously available therapies such as interferons, it comes at a cost, both in terms of impaired health-related quality of life and significant financial burden. As CML diagnosed in chronic phase (CP-CML) is “almost” a curable disease with TKI therapy, research focus has shifted towards improving health-related quality of life, management of long-term side effects, and TKI discontinuation.

Common side effects

Even though the TKIs that are currently approved for treating CML are mostly well tolerated, they are also associated with significant lifestyle changes. In general, as oncologists, we primarily pay attention to severe (grade 3) and life threatening (grade 4) adverse events. However, mild (grade 1) and moderate (grade 2) adverse events play a significant role in a patient’s daily routine given that the majority of patients will need to take these drugs indefinitely.

While many studies have not described patient-reported symptoms and functioning, Guerin et al. reported the impact of low grade adverse events (grades 1 and 2) on patient-reported health status in adult patients receiving imatinib or nilotinib in the ENESTnd trial [1]. Five low grade adverse event categories – gastrointestinal disorders, blood and lymphatic system disorders, general disorders and administrative site conditions, musculoskeletal disorders, and psychiatric disorders, were associated with reduced scores on both the generic (SF-36) and leukemia-specific (FACT-LEU) patient-reported outcome tools, in which low scores imply worse quality of life. These AEs were either lower with nilotinib or not different between the two drugs. One study demonstrated emotional/cognitive dysfunction with imatinib after 6 months of treatment, though clinically not significant [2]

Financial Toxicity

The very high costs of TKIs is a well-known issue. In 2013, an international community of CML experts voiced concerns about the cost of these drugs, which then ranged from \$92–130,000 annually [3]. Generic imatinib was introduced in 2016 at an average wholesale price of \$142,000, which was nearly the same as the \$146,000 for branded imatinib[4]. Second generation TKIs continue to be priced even higher. With an estimated 8950 new cases of CML in 2017[5], and a prevalence of 48,000, the expected costs for treatment of drug alone is approximately 5 billion US dollars annually. Not only this is a concern for society, but

financial toxicity is a serious problem for patients. In 2007, 62.1% of all US bankruptcies were attributable to medical reasons, even though three quarters of these patients had health insurance, and bankruptcies attributable to medical problems rose by 49.6%, compared to 2001 [6]. High patient costs have been associated with non-adherence to TKIs in multiple studies [7, 8].

Fertility and Pregnancy

Approximately 27% of patients diagnosed with CML are younger than 50 years old [9]. Even though imatinib does not appear to affect men's fertility, sufficient data is not available for the other TKIs [10]. Several studies have shown an increased incidence of spontaneous abortions and congenital malformations among women who become pregnant while taking a TKI [11, 12]. Based on that, the current recommendation is to discontinue TKIs for women who wish to conceive [13].

Children and adolescents as a special group

Although CML is rare in children, they are more vulnerable to the long-term toxicities of TKIs. Growth impairment is a major adverse effect with long-term imatinib treatment in children with CML who started Imatinib at a pre-pubertal age compared to those who started at pubertal age [14]. Further studies are needed to quantify this problem, particularly with newer TKIs. The most appealing strategy in this population would be to focus on true cure, rather than control of the disease with indefinite treatment.

Long-term adherence

Adherence to TKI therapy is essential for optimal disease control [15, 16]. Multiple studies have examined patient adherence to TKIs, which varies greatly depending on how adherence is defined and measured. One systematic review of adherence reported average adherence ranged from 19–100% [17], while a recent abstract reporting a meta-analysis of 40 articles and abstracts suggested adherence of 66–75% [18]. Simple forgetfulness is one known reason for non-adherence [17]. In multiple studies, older patients and those with at least 1 other comorbid condition were more adherent than others [19, 20]. It should be noted that dosing and dietary requirements for each TKI differ, e.g., imatinib needs to be taken with a big meal, nilotinib on empty stomach, and dasatinib with full glass of water [21]. Concurrent treatment of GERD with a proton pump inhibitor is contraindicated with dasatinib [22], which is another concern for some patients on this drug.

Current data supporting stopping TKIs

The first study to report TKI discontinuation was the STIM1 trial, the results of which were first published in 2010 [23] and recently updated in 2017 [24]. In the STIM1 trial, 100 adult Chronic Phase CML (CP-CML) patients with sustained Undetectable Minimal Residual Disease (UMRD, MR ^{4.5} (4.5 log reduction/BCR-ABL 0.0032%) for at least 2 years (6 times undetectable BCR-ABL transcripts, assessed by RT-PCR) with at least 3 years of treatment, discontinued TKI. Fifty of the participants had been previously treated with IFN-Alpha. With a median follow-up of 77 months for the whole study population, the rate of

treatment-free remission (TFR) was 43% at 24 months and 38% at 60 months, despite persistent leukemic cells at low levels in most, if not all patients.

Ninety-five percent of the relapses occurred in first 7 months (80% by 3 months, median 2.5 months), with no relapses after 22 months [24]. Treatment was restarted in 57 of 61 patients with molecular recurrence, 55 patients achieved a second UMRD with a median time of 4 months, and none experienced CML progression.

It was evident from the STIM1 trial that TKI discontinuation is safe and effective in many patients. However, many other questions remained unanswered, such as, who is eligible to discontinue TKIs safely? What are the factors that predict successful discontinuation? What is the right trigger to restart TKI treatment? How is the patient's health-related quality of life affected after stopping TKIs? This led to several other large discontinuation studies across the world, in an attempt to better understand the safety and feasibility of stopping TKIs.

Who is eligible to discontinue therapy?

Duration of TKI

Based on the STIM trial criteria[23], of at least 3 years on TKI therapy, this became the criteria for most studies (Tables 1 and 2). ISAV study explored minimum IM treatment duration of 24 months and showed a TFR of 51.9% at 36 months[25]. ENESTfreedom is exploring minimum 2-year treatment with front line Nilotinib (TFR of 51.6% at 48 weeks) [26]. DASfree is exploring minimum 2 years of Dasatinib, which showed a better MMR (63%) and EFS (63%) at 1 year after discontinuation[27]. No other study has evaluated further shorter TKI therapy duration. However, several studies clearly demonstrated that a longer duration of TKI therapy predicts for better TFR[28, 24]. Until further evidence is available from the current and future studies it is unlikely that a shorter duration of TKI therapy would be effective in achieving a TFR.

Depth and duration of response

As previously mentioned, the STIM trial enrolled patients who had undetectable PCR at 5 log reduction for at least 2 years[24]. More recently, the Euro-SKI[29] demonstrated that there was no difference in the rates of TFR between patients who are in MR 4, 4.5 or 5. The DESTINY trial (De- Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel in Chronic Myeloid Leukaemia) was a TKI dose reduction to half the standard dose for 12 months prior to discontinuation. The DESTINY trial was an ambitious trial enrolling patients who are at least in MR³. Based on their recently presented data, the risk of relapse is higher for patients who are in MR³[30]. Based on that the minimum response depth should be MR⁴. Most studies enrolled patients who achieved a certain level of response (e.g. MR 4 or 4.5) for at least 2 years. However, the European Stop TKI trial[29] and DADI[31] trial included patients who had a deep molecular response for one year only. In both of those studies, duration of deep molecular response did not affect rates of TFR. As most studies included patients who were in a deep molecular response for 2 years, this is the current recommendation to consider TFR. However, this criteria or requirement is very difficult to

apply and standardize clinically due to the variability of PCR testing and the considerable margin of error at low level detectable disease.

Disease phase

Limited data is available for patients who presented with accelerated or blast phase. In the ISAV (Imatinib Suspension and Validation) study[25], which included patients with accelerated phase at diagnosis, only 2 patients were enrolled with AP/BC. Specific outcomes from these 2 patients are not available. Based on that no recommendations can be made for patients with AP/BC to discontinue therapy.

Prior stem cell transplantation

Conversely the risk of resuming TKI for patients who have previously received a HCT seems lower. The KID study included 20 engrafted patients, who received Imatinib for post-transplant relapse. At a median follow-up of 15.8 months after Imatinib discontinuation, none of the 20 patients experienced UMRD loss whereas, 9 of the 28 non-transplant patients lost UMRD[32].

Sokal risk

High Sokal risk at diagnosis has been shown in multiple studies to predict high risk for molecular recurrence. For example, in the TWISTER study, three (75%) of 4 Sokal high-risk patients relapsed vs 45% of low-risk patients[33]. Similarly, in the STIM1 trial[34], high Sokal risk score was associated with increased risk of molecular relapse when compared to low and Intermediate score. However, these findings were not duplicated in the Euro-Ski trial[29], where Sokal risk correlated with TFR. In addition, outside of clinical trials very few practitioners calculate the Sokal risk and it is unknown for many patients.

Digital PCR

The ISAV study aimed at validating digital PCR to predict relapse after imatinib discontinuation in CML patients with undetectable Q-RT-PCR[25]. Patients were Monitored by standard Q-RT-PCR for 36 months. Patients resumed imatinib when they lost molecular remission. 48.1% relapsed with 73.1% in first 9 months, and 14 relapsed late between 10–22 months. Among the 56 not relapsed patients, 40 (37% of the total) regained Q-RT-PCR positivity but never lost MMR. dPCR results showed a significant negative predictive value ratio of 1.115. An inverse relationship between patients age and risk of relapse was also noticed: 95% of patients <45 years relapsed versus 42% in the class 45 to <65 years and 33% of patients ≥65 years [$P(\chi^2(2)) < 0.0001$]. Relapse rates ranged between 100% (<45 years, dPCR+) and 36% (>45 years, dPCR-) [25]. Similarly, in the A-STIM trial and KID trial, minimal residual leukemia measured by dPCR had a trend for a higher molecular relapse[35, 28, 36].

NK cells and lymphocytes as predictors of TFR

D-Stop is the prospective, multicenter discontinuation of dasatinib trial after deep MR for over 2 years and unique profiles of lymphocyte subsets for successful discontinuation in Japan[37]. This study concluded that discontinuation of dasatinib was feasible after 2- year

consolidation. Increase in lymphocytes and its subsets involving NK and NK-LGL were reported to be associated with good responses to 1st time dasatinib, these changes during consolidation after achieving DMR were negatively correlated with successful discontinuation. This unique lymphocyte changes could predict successful discontinuation. In another study by Ilander et al, patients with a higher number of NK cells and a mature NK cell subtype were more likely to stay in remission[38].

Do second generation TKIs lead to better TFR?

Several studies have evaluated the role of stopping second generation TKIs such as Nilotinib or Dasatinib. The first study report was by Rea et al[39]. In that Stop 2G-TKI study patients with CP-CML/AP-CML at diagnosis, receiving 1st or subsequent line dasatinib or nilotinib at any dose were enrolled. Of the 60 patients enrolled, 26 (43.3%) experienced a molecular relapse defined as the loss of a major molecular response (MMR). In univariate analysis, prior suboptimal response or TKI resistance was the only baseline factor associated with significantly worse outcome. The TFR for patients who were on 2G-TKI for suboptimal response/resistance vs. others was 62% vs. 23% respectively. Relapses in patients with former suboptimal response or TKI resistance failed to show any specific aggressive features compared to those occurring in patients who received 2G-TKI 1st line or after intolerance to prior therapy. In contrast, the ENESTop trial demonstrated that there was no difference in the rates of TFR in patients who switched from imatinib to nilotinib for resistance, intolerance or patients choice[40]. Multiple other studies included patients who received dasatinib or nilotinib such as DADI[31], DASfree[27], ENESTfreedom[26], ENESTgoal[41] and ENESTpath[42]. (Details in Table 2)

The ENESTfreedom[26] trial evaluated stopping nilotinib in patients with chronic phase CML who were receiving frontline nilotinib therapy for at least 2 years and were in sustained deep molecular response. Of the 190 patients enrolled, 52% of patients maintained TFR. Both the DASfree[27] study and DADI[31] trial enrolled patients who were on dasatinib either as first or subsequent line. The TFR was 63% at one year and 49% at 6 months in the DASfree and DADI trial respectively.

Several other studies are currently ongoing, evaluating switching to 2G-TKI after imatinib then stopping. In the D-STOP trial[37], patients who had undetectable disease with imatinib therapy were switched to dasatinib. Patients who maintained undetectable disease for 2 years, discontinued dasatinib therapy. Of the 65 patients enrolled, 54 maintained undetectable disease and discontinued therapy. With a median follow up of 16.2 months, the estimated TFS (treatment free survival) at one year was 63%. As expected, most relapses occurred in the first 6 months.

To date, the rates of TFR after 2nd generation TKI do not appear to be superior to imatinib. However, more patients who receive 2G-TKI will achieve a deep molecular response earlier and may be eligible to stop. In addition, a shorter treatment duration maybe sufficient with 2G-TKI as suggested by the ENESTfreedom[26] and DADI trial[31].

Can a second discontinuation be attempted?

Two studies have reported on the prospect of second discontinuation, both with very different results. In the study by Pagliardini, 67 patients who had previously discontinued to TKI and achieved another sustained deep molecular response discontinued therapy. Of those, 43% and 55% resumed TKI after first discontinuation for loss of undetectable molecular disease and loss of MMR respectively. Patients re-initiated TKI with loss of MMR in the second discontinuation. With a median follow up of 21.5 months, 44% of patient remained in MMR and did not restart drug[43]. In contrast, in another study by Matsuki et al, patients with CML-CP who had previously attempted discontinuation, and restarted for a PCR level > 100 attempted a 2nd discontinuation. Of the 10 patients who were enrolled, all but one patient lost MMR and restarted the drug[44]. The most likely explanation for the markedly different results is the trigger for the first restart. In the study by Pagliardini, 43% restarted the first time when the PCR was detectable. The second restart was triggered by loss of MMR. So, it is possible that many of those patients would not have needed to restart the first time (17). In the long term follow up of the STIM trial, 15 patients attempted a second discontinuation. Of those, 5 needed to restart therapy[45, 34]

What is the appropriate Trigger to restart TKI?

The trigger to restart TKIs has differed in various studies. After realizing that some patients may have persistent detectable disease, but have no evidence of disease progression, the threshold for restarting TKI was raised. The A-STIM trial was the first study to restart TKI at loss of MMR[46].

The A-STIM (According to Stop Imatinib) was a multicenter observational Study, which evaluated the safety of Major Molecular Response (MMR) loss as a trigger for restarting tyrosine kinase. Of the 80 patients with CP-CML enrolled, 29 patients (36%) lost MMR after a median of 4 months off therapy. Fluctuation of BCR-ABL transcript levels below the MMR threshold was observed in 31% of patients after discontinuing Imatinib. Treatment-free remission was 64% at 12 and 24 months and 61% at 36 months. Based on that data, several studies used loss of MMR as the trigger to restart TKI [46]. Although definition of MR (molecular relapse) leading to treatment resumption was slightly different in various stopping TKI studies, common feature is most cases of Molecular Recurrence occur during the first few months (mainly up to 6 months) after Imatinib cessation. Based on that monthly PCR testing is recommended in the first 6 months of therapy.

TKI Withdrawal syndrome

TKI withdrawal syndrome, a musculoskeletal pain syndrome was first described by Richter et al, from the EURO-SKI study. The musculoskeletal pain (muscle tenderness, sometimes resembling polymyalgia rheumatica) began or worsened within 1–6 weeks after stopping imatinib therapy in about 30% (15 out of first 50) of patients. Median duration of imatinib therapy was 9 years, the severity was graded 1–2[47]. Therapy is mainly supportive with NSAIDs and/or steroids. Symptoms also rapidly resolved in patients who restarted imatinib. Similarly, in the KID study musculoskeletal pain after IM discontinuation occurred in

approximately 30% of patients, though no patient was restarted on imatinib due to musculoskeletal pain. Interestingly, patients who develop imatinib withdrawal syndrome were more likely to remain in remission [36].

Conclusion and Future directions

Available data suggest that most patients will need to continue TKI indefinitely. For 100 newly diagnosed patients, about 50% will achieve a deep molecular response. Of those, approximately 25 (50%) will need to restart therapy. Based on that, 75% of patients with CML will require lifelong tyrosine kinase inhibitor therapy. Some may argue that, given patients have a normal life expectancy on TKI therapy, no more research is needed in CML. However, that is not true for all patients and treating physicians. Better therapies are needed to eradicate CML and truly cure more patients with CML, that is, patients are off drug with no evidence of disease. Several compounds are effective in the therapy of CML. CML is an immune sensitive disease, therefore, immunotherapies (e.g. PD-1 inhibitors and NK cell activators) may have a future role in CML therapy. Other possibilities include proteasome inhibition, bcl-2 inhibition, TKI combinations, and ABL-001. In order to move CML research forward, several investigators in the US are collaborating to form a CML consortium with the ultimate goal of curing this disease.

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Table 1

Selected Imatinib only Discontinuation Studies, their Characteristics and Important Findings

Study	Number of Patients	TKI	TFR % (Approximate Years)	Comments
STIM1[24] (STop Imatinib 1)	100	Imatinib ($\pm$ Prior Interferon)	TFR: 38%(5 Y)	Sokal Risk and Imatinib duration were associated with probability of MR (Molecular Recurrence)
A-STIM[48] (According to STop Imatinib)	80	Imatinib ($\pm$ Prior Interferon)	TFR: 61%(3 Y)	Similar Criterion as STIM trial with exception of including patients with confirmed CMR with occasional positive samples before study entry. Loss of MMR is a practical and safe criterion for restarting therapy
TWISTER[49] (Trial of Withdrawal of Imatinib therapy in adult patients with CP-CML in Stable Molecular Remission)	40	Imatinib ($\pm$ Prior Interferon)	TFR:47%(2 Y)	Found no advantage with q3month BM qRT-PCR than PB monitoring
ISAV[25] (Imatinib Suspension And Validation Study)	112	Imatinib ($\pm$ Prior Interferon)	TFR:51.9%(3 Y)	Most relapsed within 9months after Imatinib discontinuation; Age <45y, dPCR positivity is associated with higher likelihood of relapse.
KIDS[28] (Korean Imatinib Discontinuation Study)	90	Imatinib ($\pm$ Prior interferon)	TFR:58.5%(2 Y)	Imatinib withdrawal syndrome in 30% of those who discontinued Imatinib; Imatinib withdrawal syndrome is associated with high probability of sustained MMR

Table 2

Selected Other Tyrosine Kinase Inhibitor Discontinuation Studies Including Imatinib, their characteristics and Important findings

Study	Number of Patients	TKI	TFR %(Approximate Years)	Comments
ENESTgoal[41] (Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Switch to Nilotinib and Stop Treatment After Achieving and Sustaining MR ^{4.5} .)	59	Imatinib MR3 then switch to Nilotinib	N/A	66% of pts with MMR but not MR ^{4.5} on IM achieved confirmed MR ^{4.5} after switching to Nilo.
ENESTpath[50] (ENEST– To Assess the Effect of a Longer Duration of Consolidation Treatment with Nilotinib on TFR in CP CML)	620	Imatinib then Nilotinib	N/A	Switch to Nilo at 300mg bid, induces high rates of MR ⁴ and MR ^{4.5} in pts without such MR on IM
ENESTfreedom[26] (ENEST– Nilotinib Treatment-FREE Remission Study in CML Patients.)	190	Nilotinib	TFR:51.6%(1 Y)	Studied in front line Nilo patients
ENESTop[40] (ENEST–STOP Nilotinib)	126	Imatinib to Nilotinib	TFR:57.9%(1 Y)	Rate of TFR following 2 nd line Nil does not differ based on reasons for switching from Imatinib to Nilotinib
EURO-SKI[29] (EUROpean Stop Tyrosine Kinase Inhibitor Study)	868	Imatinib, Nilotinib, Dasatinib	TFR: 52%(2 Y)	Largest trial to date. Longer duration of Imatinib therapy (5.8 y) is associated with high probability of MRFS.
STOP2G-TKI[39] (STOP second generation (2G) Tyrosine Kinase Inhibitor (TKI))	60	Dasatinib, Nilotinib (±Prior Interferon)	TFR:53.7% (4 Y)	Prior suboptimal response or TKI resistance is the only baseline factor associated with significantly worse outcome. Loss of MR ^{4.5} , 3 months after stopping 2G-TKI was predictive of failure to maintain MMR later
DADI[31] (Dasatinib Discontinuation trial)	63	2 nd or subsequent line Dasatinib	TFR: 49%(0.5 Y)	Dasatinib discontinuation is feasible after sustained DMR for 1 year

Study	Number of Patients	TKI	TFR %(Approximate Years)	Comments
D-STOP[37] (Dasatinib STOP Trial)	54	Dasatinib	TFR: 62.9%(1 Y)	Unique profile of lymphocyte subsets might be able to predict successful discontinuation
Pagliardini et.al (FiLMC group) [43]	67	2 nd TKI discontinuation who failed 1 st discontinuation	TFR after 2 nd TKI discontinuation:44%(1.8 Y)	Median duration of 1 st CMR:35 months
Matsuki et al[44]	53	Dasatinib 2 nd discontinuation	TFR: 52.8%(2 Y) with 1 st DC of TKI TFR of 20% at 2 years with 2 nd DC of TKI	2 nd Attempt to discontinue TKI is much less successful
DasFree[27] (DASatinib FREE: Dasatinib discontinuation in CP-CML With Stable CMR)	71/79	Dasatinib 1 st or 2 nd line	TFR: 63%(1 Y after DC)	Longer duration on Dasatinib prior to DC is associated with higher rates of retained MMR (63% at 1 Y)
TRAD[51] (Treatment-free Remission Accomplished with Dasatinib in Patients With CML)	75/135	Imatinib Dasatinib (±Hydroxyurea, anagrelide or interferon)	N/A	Initial Imatinib discontinuation, dasatinib re-challenge, dasatinib discontinuation
NILSt[52] (Stop Nilotinib Trial)	90	Imatinib or nilotinib then Nilotinib for 2 years	TFR:58.9%(1 Y)	Period of deep MR after which Nilotinib can be discontinued without relapse is considerably long, cannot predict relapse free survival
STAT2[53] (Stop TASIGNA Trial)	96	Imatinib then 2 years Nilotinib	TFR:62.5% in Imatinib front line group (1 Y) TFR:69.7% in Nilotinib 2 nd line after Imatinib (1 Y)	No significant differences between the two groups
LAST[54] (The Life After Stopping Tyrosine Kinase Inhibitors Study)	173	Imatinib, Dasatinib, Nilotinib, Bosutinib	N/A	Concurrently assessing wide range of PROs before and after stopping TKIs

AP: Accelerated Phase; CP: Chronic Phase; CML: Chronic Myeloid Leukemia; DPCR: Digital Polymerase Chain Reaction; PRO: Patient related outcomes; TKI: Tyrosine kinase Inhibitor; IM: Imatinib; Nilo: Nilotinib; TFR: Treatment Free Remission; EFS: Event Free Survival; MR: Molecular remission; MMR: Major Molecular Response; MRFS: Molecular Remission Free Survival; N/A: Not available/Not applicable; CMR: Complete Molecular Remission; DFS: Drug Free Survival; DMR: Deep Molecular Response