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CHRONIC MYELOID LEUKEMIAS (M MAURO, SECTION EDITOR)

Treatment-Free Remission in CML: the US Perspective

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Abstract

Purpose of Review Chronic myeloid leukemia (CML) patients treated with tyrosine kinase inhibitors (TKI) have near-normal life expectancy. However, lifelong TKI therapy is associated with reduced quality of life and significant economic burden. Currently, the management of CML is shifting from continuous TKI therapy towards the goal of TKI cessation which is discussed in this review.

Recent Findings Several studies in the last decade have demonstrated the feasibility and safety of TKI discontinuation in selected patients with CML who achieve deep and sustained molecular response with TKI. This has moved prime-time into clinical practice although open questions remain in terms of understanding the disease biology that leads to successful TKI cessation in some patients while not in others.

Summary Cessation of TKI for CML patients is a feasible approach. Ongoing research aims to find out optimal strategies to sustain ongoing treatment-free remission (TFR) and increase the number of patients who achieve TFR.

Keywords Leukemia · Myeloid · Chronic · Treatment · Discontinuation

Introduction

The outlook of chronic myeloid leukemia (CML) has changed dramatically after the introduction of tyrosine kinase inhibitors (TKI). CML, which was once viewed as an aggressive malignancy with poor outcomes, has now become a chronic medical illness where the disease could be controlled with long-term TKI therapy. In fact, studies demonstrated that the life expectancy of CML patients is near normal as compared to the general population in the TKI era [1]. Even though treatment discontinuation after achieving a target control is rarely entertained in other common chronic medical conditions such as diabetes or hypertension, it has been an important area of investigation in patients with CML. The cost of the therapy, side effects associated with long-term use of TKIs, patient's decline in the quality of life (QOL), and anxiety of being on long-term cancer treatment are several reasons that galvanize the ongoing research focused on TKI discontinuation. In fact, when we consider the near-normal relative survival of CML patients in the current era, the prevalence of CML is increasing and is expected to reach around 180,000 patients around 2050 [2]. This increase in disease prevalence potentially increases the cost associated with therapy from a population perspective. Currently, the concept of treatment-free remission (TFR) has started trickling from the research setting into practice with the incorporation of TKI discontinuation in the national comprehensive cancer network (NCCN) guidelines in the United States (US) [3••]. However, this is still an area of active research with many unanswered questions. In this review, we will discuss the current available literature that helps in the decision making for TKI discontinuation and the unique aspects for patients from the US.

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Concept of TFR

TFR centers on the duration of molecular remission that could be maintained in patients with CML after cessation of TKI therapy. The current standard assay for monitoring patients with CML involves a quantitative polymerase chain reaction

assay (PCR) to measure the burden of BCR-ABL transcripts. In this context, molecular remission (MR) has been defined using various thresholds. Major molecular remission (MMR) refers to achievement of a 3 log reduction in the BCR-ABL transcript load (0.1%). Further deep remissions are achievable to the level of 4 log reduction (MR 4 or 0.01%), 4.5 log reduction (MR 4.5 or 0.0032%), and 5 log reduction (MR 5.0 or 0.001%) based on the sensitivity of the assay. Achievement of MMR is an important goal in the first 2 years of therapy with TKI [3••]. For patients treated with frontline imatinib, MMR of 22–36% is achieved in the first 12 months [4–6]. Similarly, for patients treated with frontline dasatinib, nilotinib, or bosutinib therapy, a MMR of 46%, 44%, and 47.2% respectively is achievable within 12 months of therapy [4–6]. It is important to note that the proportion of patients who achieve deep MR increases with time. For example, about 20% patients treated with frontline imatinib achieve MR4.5 in the first 2 to 3 years of therapy, but increases to 40% after 5 to 7 years of continued therapy [7]. This reflects an increase in the proportion of patients over time who would become eligible for TKI discontinuation. Even though these patients remain in sustained deep MR, there is evidence suggesting continued presence of CML stem cells [8].

US Perspective for TKI Discontinuation

Patient Perspective

While discontinuing TKI appears to be feasible from the research perspective, it may or may not hold true when it comes to patient decision. Limited studies in the US have so far explored patient perspectives of TKI discontinuation. A study by Goldberg et al. reported a survey from a cohort of 210 CML patients treated at a single center [9]. They found that only 42% of patient were willing to try TKI discontinuation, with 34% of patients preferring to continue TKI therapy, and 25% of patients being undecided. The reasons expressed by patients to discontinue TKI were side effects (40%), costs (30%), and inconvenience (26%). Similarly, the reasons given by patients for not willing to attempt TKI discontinuation were possible disease recurrence (58%) and lack of current toxicities (17%). They also noted that a higher proportion of patients (67%) were willing to discontinue TKI if the success rate was 60% and salvageable relapse was 40%, as opposed to a lower proportion (58%) willing to discontinue TKI if success was 50% and salvageable relapse was 50%. Another study by Flynn et al. reported on 20 CML patients with deep MR from 3 academic medical centers and found that most participants mentioned their doctor's advice as key to their decision to stop or continue TKI in addition to other factors such as reduction in the number of medications, in side effects, and financial burden [10]. Patients who wanted to continue TKI mentioned reasons such as avoiding the chance of relapse and fear of losing their access to free/reduced price drugs if they stopped. More recently, George et al. reported on a survey of 458 CML patients with 26% of them having previously stopped TKI for at least 1 month [11]. When presented with the possibility of stopping all future treatment for CML with additional treatment, they found that 97% of them were willing to add another oral medication to their TKI while 89% of patients were willing to accept intravenous treatment in addition to a TKI. Half of the patients had discussed treatment discontinuation with their physician, with 45% considering this option in an attempt at TFR. Hence, variations in acceptance of TKI discontinuation by patients depend on several of the aforementioned factors which need to be considered when designing new clinical studies.

Physician Perspective

Physician's perspective of TKI discontinuation plays an important role in the decision making and providing appropriate advice to these patients. Even prior to the availability of clinical guidelines for cessation of TKI, there is evidence that clinicians were interested in TKI cessation and were attempting it under certain circumstances. A study by Ritchie et al. reported on a survey among US practitioners to assess the practice of TKI discontinuation before the publication of new practice guidelines [12]. The study revealed that physicians who reported TKI discontinuation were more likely to practice in academic centers, be experienced clinicians, and followed a larger number of CML patients. In addition, the reasons for TKI discontinuation included more medical reasons (76% adverse events, 47% pregnancy planning), relatively lesser economic reasons (35%), and 12% of them were willing to consider it for all patients who achieve an adequate response. However, there was no consensus found about the minimal duration of therapy or minimal response needed prior to TKI cessation attempt. That study highlighted the importance of physician education on eligibility for TKI discontinuation, proper monitoring, and when to restart therapy.

Health Economics Perspective

Cost associated with therapy is an important factor for considering TKI discontinuation in the US. It is more expensive to treat CML patients in the US as compared to other countries with an estimated annual cost of TKI therapy ranging from $118,000–$138,000 with patients paying an average of 20% out-of-pocket cost [13•]. A recent study by Winn et al. using SEER-Medicare database demonstrated that patients with CML who had to spend more out-of-pocket cost were more likely to be non-adherent with TKI therapy [14]. Hence, the financial burden of lifelong TKI therapy cannot be understated. Prior to the availability of NCCN guidelines for TKI

cessation, studies from the US attempted to assess the cost effectiveness of various TKIs in the initial management of CML. A study by Padula et al. demonstrated that using first-line imatinib would be more cost effective as compared to physician's choice of initiating any other TKI due to the fact that imatinib would be cheaper after losing its patent protection [15]. In the current era, another important way of looking at the cost effectiveness would be to initiate a second-generation TKI for newly diagnosed CML which could produce quicker and deeper MR enabling patients to be eligible for TKI discontinuation at some point, thereby offsetting the financial burden of therapy down the road in the course of CML. However, with the current cost of second-generation TKIs (approximately $100,000/year) compared to the expected cost of generic imatinib (approximately $10,000), this approach does not seem to be cost effective. Using a simple calculation of second-generation TKI cost effectiveness for discontinuation, the cost would be approximately $60 million over 10 years for an extra 10 patients to achieve TFR. Of every 100 patients treated with imatinib, approximately 30 will achieve MR4 at 5 years and of those 50% will maintain TFR. Therefore, 85 patients will require lifelong TKI therapy. If the cost of generic imatinib in the US decreases to $10,000/year, then over a 10-year period the cost for 100 patients will be $10,000 × 85 patients × 10 years = 8.5 million. Of 100 patients who start on a 2nd-generation TKI, approximately 75 will require lifelong TKI therapy (50% achieve MR4 and of those, 50% maintain TFR). The cost over a 10-year period would be $100,000 × 75 patients × 10 years = $75 million.

Evolving Recommendations for Clinical Practice

Currently, the NCCN guidelines have provided recommendations on eligibility and monitoring for patients who attempt TKI discontinuation [3••]. According to the NCCN guideline, TKI cessation can be considered when all these criteria are met—patients with age ≥ 18 years, chronic phase CML and no prior history of accelerated phase/blast phase, presence of a quantifiable BCR-ABL transcript, treatment with TKI for at least 3 years with minimum 2 years of stable MR4.0, and access to reliable Q-PCR monitoring during follow-up. After satisfying these criteria, a detailed discussion about the benefits and risks associated with TKI cessation is to be discussed with the patient and then considered for TFR attempt. During the TFR period, it is recommended to have monthly monitoring with q-PCR for 1 year, followed by every 6 weeks monitoring for the second year and every 12 weeks thereafter, indefinitely while being off TKI. However, open questions still remain about the optimal depth of response, duration of therapy prior to TKI cessation and frequency of monitoring after TKI cessation, and the recommendations continue to evolve. As an example, in December 2017, FDA updated its label for nilotinib with indications for therapy discontinuation for patients who have been on therapy for 3 years, have achieved a sustained MR4.0 (BCR-ABL1 International Scale ≤ 0.01%, typical BCR-ABL transcript) for 1 year only, and achieved an MR4.5 (BCR-ABL1 International Scale ≤ 0.0032%, typical BCR-ABL transcript) for the last assessment prior to TKI discontinuation [16].

Trials in the US to Date

Several phase 2 clinical trials performed in the US have demonstrated that discontinuation of TKI is feasible in patients with sustained deep MR as summarized in Table 1. The feasibility of TKI cessation exclusively in the US population is being studied in the LAST study (NCT 02269267) [21•]. This is a non-randomized, prospective, longitudinal study of 173 patients. The co-primary objectives are to determine the proportion of patients who develop molecular recurrence (> 0.1% BCR-ABL-IS) after discontinuing one of four TKIs (imatinib, dasatinib, nilotinib, or bosutinib) and to compare the patient-reported health status of patients before and after stopping TKIs. Preliminary results of this study were presented recently. With a median follow-up of 12.3 months, the TFR rate was 61%. The TFR rate at 6 and 12 was 73% and 60% respectively [22]. This study will provide more information on the impact of TKI cessation on patient's QOL and the role of digital PCR–based monitoring.

Several studies are exploring the possibility of combining TKI with another agent in order to improve the depth and durability of MR achieved, thereby improving the TFR duration. One of the pathways which serve as a protective microenvironment for the CML stem cells is the phosphorylation of STAT3-Y705 via the JAK-STAT signaling pathway and this could be targeted through inhibition JAK2 and TYK2 using agents such as ruxolitinib. A phase I study by Sweet et al. reported on the combination of nilotinib with ruxolitinib demonstrating a 44% probability of achieving MR4.5 after 6 months surpassing that of historical controls [23]. Additional clinical trials examining the role of ruxolitinib for patients who are not in a deep molecular remission (NSC-752295) and for those trying to attempt a second TFR (NCT03610971) are ongoing. In addition, pembrolizumab, an immune checkpoint inhibitor blocking the PD-1/PDL-1 pathway, is being tested in combination with either imatinib, dasatinib, or nilotinib to eradicate minimal residual disease through a phase II cooperative group trial (NCT03516279). BCL-2 inhibition is another pathway currently being explored to increase the percentage of patients achieving a deep molecular response, ultimately leading to a TFR (NCT02689440) [24].

In this context, an important step has been taken towards fostering collaborative research in CML in the US. The H. Jean Khoury Cure CML Consortium was established in 2016 with participation from several academic medical

Table 1 Major studies on TKI cessation in the US

Study	Number of patients	Key criteria	Outcomes	Predictive factors
ENESTfreedom [17]	190	-CML-CP -Frontline nilotinib for at least 2 years and achieved MR4.5 -Underwent 1-year nilotinib consolidation -Loss of MMR as retreatment trigger	TFR: 51.6%(48 weeks)	No significant predictors identified
ENESTop [18]	126	-CML-CP -TKI for 3 years and achieved MR4.5 after switching from imatinib to nilotinib -Entered nilotinib consolidation for 1 year prior to cessation	TFR: 53%(96 weeks)	Time from achievement of MR4.5 on nilotinib to TKI cessation
ENESTgoal [19]	59	CML-CP who had MMR but not MR4.5 after ≥ 1 year of imatinib, switched to nilotinib for 2 years, followed by TKI cessation in those with no confirmed loss of MR4	66% of pts. with MMR but not MR4.5 on IM achieved confirmed MR4.5 after switching to nilotinib	None reported
DasFree [20]	71/79	-CML-CP -Dasatinib for 2 years -MR 4.5 for 1 year -At least 1 log reduction within 3–6.5 months of dasatinib	MMR/EFS: 63%(1 year)	Time on dasatinib prior to cessation
LAST[21•, 22]	173	-CML-CP on TKI (imatinib, dasatinib, nilotinib, or bosutinib) -MR4.0 for 2 years	TFR: 73% (6 months) and 60% (12 months)	Concurrently assessing wide range of PROs before and after stopping TKIs

AP accelerated phase, *CP* chronic phase, *CML* chronic myeloid leukemia, *TKI* tyrosine kinase Inhibitor, *TFR* treatment-free remission, *EFS* event-free survival, *MR* molecular remission, *MMR* major molecular response, *PRO* patient-reported outcomes

centers committed to CML research and improving patient care. Studies are being planned through this consortium to test novel hypothesis and improve the success of TKI cessation.

Conclusions

We have currently moved prime-time into an era where TKI cessation could be considered for CML patients in the US with deep and sustained MR while on TKI. While the inclusion of TKI cessation criteria in the NCCN guidelines is a tremendous start, many questions continue to remain in terms redefining the criteria for TKI cessation, understanding the disease biology that leads to successful TFR in some patients while not in others, and strategies to sustain ongoing TFR and increase the number of patients who achieve TFR. There are preliminary signals that TKI cessation and TFR attempt could improve the QOL and financial burden of patients with CML. Ongoing studies are expected to provide more information that would enhance the clinical decision-making process while considering TKI cessation.

Compliance with Ethical Standards

Conflict of Interest Ehab Atallah reports personal fees from Novartis, BMS, and Pfizer, outside the submitted work. Guru Subramanian Guru Murthy declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. 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(5):e186–93. https://doi.org/10.1016/S2352-3026(15)00048-4.
2. Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer. 2012;118(12):3123–7. https://doi.org/10.1002/cncr.26679.
3. •• NCCN Clinical practice guidelines in oncology. Chronic myeloid leukemia version 4.2018 - Jan 24, 2018. **First practice guidelines in US for TKI cessation.**
4. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362(24):2260–70. https://doi.org/10.1056/NEJMoa1002315.
5. Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362(24):2251–9. https://doi.org/10.1056/NEJMoa0912614.
6. Cortes JE, Gambacorti-Passerini C, Deininger MW, Mauro MJ, Chuah C, Kim DW, et al. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial. J Clin Oncol. 2018;36(3):231–7. https://doi.org/10.1200/JCO.2017.74.7162.
7. Branford S, Seymour JF, Grigg A, Arthur C, Rudzki Z, Lynch K, et al. BCR-ABL messenger RNA levels continue to decline in patients with chronic phase chronic myeloid leukemia treated with imatinib for more than 5 years and approximately half of all first-line treated patients have stable undetectable BCR-ABL using strict sensitivity criteria. Clin Cancer Res. 2007;13(23):7080–5. https://doi.org/10.1158/1078-0432.CCR-07-0844.
8. Chomel JC, Bonnet ML, Sorel N, Bertrand A, Meunier MC, Fichelson S, et al. Leukemic stem cell persistence in chronic myeloid leukemia patients with sustained undetectable molecular residual disease. Blood. 2011;118:3657–60. https://doi.org/10.1182/blood-2011-02-335497.
9. Goldberg S, Hamarman S. Patients with chronic myelogenous leukemia may not want to discontinue tyrosine kinase inhibitor therapy. Blood. 2015;126:1584 (abstract).
10. Flynn K, Schiffer C, Thompson J, Atallah E. Patient decision making about treatment discontinuation. Presented at ESH John Goldman Conference on CML, 2016 (abstract).
11. George G, Atallah E, Mauro M et al. Patients' perspectives on the definition of cure in chronic myeloid leukemia: a US based survey. Accepted for ESH John Goldman Conference on CML, Sep 2018 (abstract).
12. Ritchie EK, Wolff JE, Latremouille-Viau D, et al. Tyrosine kinase inhibitor (TKI) therapy discontinuation in patients with CML in chronic phase: a US clinical practice perspective. J Clin Oncol. 2017;35(15):7052 (abstract).
13. • Abboud C, Berman E, Cohen A, 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. https://doi.org/10.1182/blood-2013-03-490003 **Highlights the importance of the financial burden of TKI therapy**.
14. Winn AN, Keating NL, Dusetzina SB. Factors associated with tyrosine kinase inhibitor initiation and adherence among Medicare beneficiaries with chronic myeloid leukemia. J Clin Oncol. 2016;34(36):4323–8. https://doi.org/10.1200/JCO.2016.67.4184.
15. Padula WV, Larson RA, Dusetzina SB et al. Cost-effectiveness of tyrosine kinase inhibitor treatment strategies for chronic myeloid leukemia in chronic phase after generic entry of imatinib in the United States. J Natl Cancer Inst. 2016;108(7). doi: https://doi.org/10.1093/jnci/djw003
16. Accessed https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022068s026lbl.pdf
17. Hochhaus A, Masszi T, Giles FJ, Radich JP, Ross DM, Gomez 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. https://doi.org/10.1038/leu.2017.63.
18. 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. https://doi.org/10.7326/M17-1094.

19. Ritchie EK, Catchatourian R, Klisovic RB, Pinilla-Ibarz J, Deininger MW, Erba HP, et al. ENESTgoal treatment-free remission study: updated preliminary results and digital polymerase chain reaction analysis in patients with chronic myeloid leukemia in chronic phase who switched from imatinib to nilotinib. Blood. 2016;128(22):3090 (abstract).
20. Shah NP, Paquette R, Müller MC, Saussele S, Garcìa-Gutiérrez V, Jiménez-Velasco A, et al. Treatment-free remission (TFR) in patients with chronic phase chronic myeloid leukemia (CML-CP) and in stable deep molecular response (DMR) to dasatinib—the Dasfree study. Blood. 2016;128(22):1895 (abstract).
21.• Atallah E, Schiffer CA, Weinfurt KP, et al. Design and rationale for the life after stopping tyrosine kinase inhibitors (LAST) study, a prospective, single-group longitudinal study in patients with chronic myeloid leukemia. BMC Cancer. 2018;18(1):359. https://doi.org/10.1186/s12885-018-4273-1 **An important prospective study from US looking at various aspects of TKI cessation**.
22. Atallah E, Schiffer CA, Radich JP, Weinfurt K, Zhang MJ, Kota K, et al. Results from the U.S. Life after Stopping TKIs (LAST) Study. Blood. 2017;130(s1):2903 (abstract).
23. Sweet KL, Hazlehurst L, Sahakian E, et al. A phase I study of ruxolitinib plus nilotinib in chronic phase CML patients with molecular evidence of disease. Blood. 2016;128(22):1892 (abstract).
24. Carter BZ, Mak PY, Mu H, et al. Combined targeting of BCL-2 and BCR-ABL tyrosine kinase eradicates chronic myeloid leukemia stem cells. Sci Transl Med. 2016;8(355):355ra117. https://doi.org/10.1126/scitranslmed.aag1180.