Curr. Treat. Options in Oncol. (2021) 22: 49
DOI 10.1007/s11864-021-00851-2

Leukemia (PH Wiernik, Section Editor)

When to Stop TKIs in Patients with Chronic Myeloid Leukemia and How to Follow Them Subsequently

Nuno Cerveira, PhD[1,*]
Susana Bizarro, MsC[1]
Manuel R. Teixeira, MD PhD[1,2]
José M. Mariz, MD[3]

Address
[*,1]Serviço de Genética, Instituto Português de Oncologia do Porto, Rua Dr. António Bernardino de Almeida, 4200-072, Porto, Portugal
Email: nuno.cerveira@ipoporto.min-saude.pt
[2]Instituto de Ciências Biomédicas, Universidade do Porto, Porto, Portugal
[3]Serviço de Hematologia, Instituto Português de Oncologia do Porto, Porto, Portugal

Published online: 17 April 2021

This article is part of the Topical Collection on *Leukemia*

Keywords Chronic myeloid leukemia · Treatment-free remission · Treatment discontinuation · TKI discontinuation

Opinion statement

ABL1 tyrosine kinase inhibitors (TKI) have dramatically improved the outcome for CML (chronic myeloid leukemia) patients. When TKI therapy is addressed appropriately, it can lead to an optimal molecular response in the majority of CML patients and a life expectancy that approaches that of the general population. However, lifelong TKI therapy may have consequences, including chronic, mostly low-grade, adverse events that can substantially impact patients' quality of life, adherence to therapy and, consequently, success of treatment. In the last few years, several groups have demonstrated that approximately 50% of chronic phase CML patients (CP-CML) who have achieved a stable deep molecular response (DMR) can stop therapy without suffering molecular relapse. Nowadays, treatment-free remission (TFR) has a significant role in the management of CML and should be considered in selected motivated patients that fulfill well-defined requirements to maximize the probability of successful discontinuation of TKI therapy.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasia caused by the fusion of the *BCR* and *ABL1* genes, most frequently as the result of the reciprocal translocation t(9;22)(q34;q11). The resulting *BCR-ABL1* gene fusion codes for a tyrosine kinase with aberrant activity that drives multiple downstream signaling pathways, leading to increased proliferation and genomic instability with decreased apoptosis [1]. ABL1 tyrosine kinase inhibitors (TKIs) have dramatically improved the outcome for CML patients. Indeed, when TKI therapy is addressed appropriately, it can lead to an optimal molecular response in the majority of CML patients and a life expectancy that approaches that of age-matched individuals in the general population [2]. Several TKIs are approved for the treatment of CML, including first-line inhibitor imatinib; second-line inhibitors dasatinib, nilotinib, and bosutinib; and third-line inhibitor ponatinib. For the selection of the most appropriate therapy for individual patients, several factors must be taken into account, including efficacy, patient comorbidities, tolerability, early and late toxicity, and drugs costs. Until recently, the main goal of CML therapy was disease control with the best possible overall survival (OS) but with lifelong treatment. However, lifelong TKI therapy may have consequences, including chronic, mostly low-grade, adverse events that can substantially impact patients' quality of life, adherence to therapy, and, consequently, success of treatment [3]. More recently, the paradigm for CML management has gradually changed to increase the quality of life, to minimize long-term organ toxicities, and to identify strategies to maximize the possibility of treatment-free remission (TFR), i.e., to stop TKI therapy [3]. Indeed, long-term treatment-free remission with sustained deep molecular response (DMR) off TKI therapy is nowadays considered the most optimal aim of CML treatment.

Definitions and relevance of molecular response in CML

Most patients receiving TKIs achieve a complete cytogenetic response, warranting more sensitive approaches for monitoring residual disease with reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) to estimate the amount of *BCR-ABL1* mRNA relative to an internal reference gene (Table 1) [4, 5••]. *BCR-ABL1* levels should be expressed on the International Scale (IS) as a percentage relative to a consensus baseline value used in the IRIS (International Randomized Study of Interferon and STI571) trial [6]. This only applies to CML patients that present with typical *BCR-ABL1* transcripts (e13a2 and e14a2), which can be found in approximately 98% of patients with CML [7]. This implies that the remaining patients with atypical rearrangements cannot have their *BCR-ABL1* levels expressed on the IS. A major molecular

Table 1. Definitions of molecular response in patients with CML [4, 5••]

BCR-ABL1 transcript level IS (%)	Molecular response level	Minimum number of *ABL1* transcripts	Minimum number of *GUSB* transcripts
100	-	-	-
≤0.1	$MR^{3.0}$ (MMR)	>10,000	>24,000
≤0.01	$MR^{4.0}$	10,000–31,999	24,000–76,999
≤0.0032	$MR^{4.5}$	32,000–99,999	77,000–239,999
≤0.001	$MR^{5.0}$	≥100,000	≥240,000

CML chronic myeloid leukemia, *IS* International Scale, *MR* molecular response, *MMR* major molecular response

response (MMR) is defined as a 3-log reduction from the standardized baseline ($MR^{3.0}$ or *BCR-ABL1*^{IS} ≤0.1%), which is an important step toward a favorable outcome. Indeed, stable MMR represents a solid surrogate marker for long-term progression-free survival [3]. However, patients in MMR but who do not achieve a DMR must receive TKIs indefinitely to maintain CML under control because the likelihood of TFR is unlikely [4]. With prolonged TKI therapy, deeper levels of response can be achieved, with some patients reaching levels where no disease can be detected. Laboratory recommendations for scoring deep molecular response (DMR) are defined as $MR^{4.0}$ (either detectable disease ⩽0.01% *BCR-ABL*^{IS} ($MR^{4.0}$ positive) or undetectable disease in cDNA with 10 000–31 999 *ABL1* transcripts or 24 000–76 999 *GUSB* transcripts ($MR^{4.0}$ negative)), $MR^{4.5}$ (either detectable disease ⩽ 0.0032% *BCR-ABL*^{IS} ($MR^{4.5}$ positive) or undetectable disease in cDNA with 32 000–99 999 *ABL1* transcripts or 77 000–239 999 *GUSB* transcripts ($MR^{4.5}$ negative)), and $MR^{5.0}$ (either detectable disease ⩽ 0.001% *BCR-ABL*^{IS} ($MR^{5.0}$ positive) or undetectable disease in cDNA with ⩾100 000 *ABL1* transcripts or ⩾240 000 *GUSB* transcripts ($MR^{5.0}$ negative)) (Table 1) [4, 5••]. Achieving and maintaining a DMR is particularly important for the long-term success of TKI discontinuation, defined as the patient remaining in DMR or at least in MMR [5••].

Clinical trials of TKI discontinuation

In 2007, the French CML group published a seminal study of 12 patients with no detectable disease evaluated by RTq-PCR for more than 2 years that discontinued imatinib treatment [8]. They found that 50% of the patients remained in molecular remission with undetectable *BCR-ABL1* levels [8]. The first prospective trial for discontinuation TKI treatment was the STIM (STtop IMatinib) trial, which showed that 38% of the patients maintained a molecular remission after a median follow-up of 77 months (Table 2) [9••, 10]. The eligibility criterion for interrupting treatment was no detectable disease, corresponding to a molecular response of around $MR^{4.5}$ sustained for at least 2 years before stopping [9••]. In this trial, molecular relapse was defined as two positive RT-qPCR results over a period of 1 month, which was a trigger for restarting imatinib treatment [9••]. Since then, multiple trials have been conducted in an attempt to explore the result of ceasing TKI therapy in highly selected patients, including not only in patients treated with imatinib but also in patients treated with second-generation TKIs (2G-TKI) such as dasatinib and nilotinib, which used slightly different entry criteria and different triggers to restart TKI treatment (Table 2) [10–14, 15•, 16–18, 19••, 20–31]. A recent meta-analysis of 29 studies that included 3105 patients showed a probability of molecular recurrence after TKI cessation of 49%, illustrating the high reproducibility of the results [32]. Most molecular relapses occurred during the first 6 months of a first TFR attempt, emphasizing the need for frequent monitoring and follow-up during this early period, whereas the molecular recurrence after a second TFR attempt is not only more frequent but also seems to occur over a wider window of time [32]. Importantly, a large body of evidence has demonstrated that, provided proper residual disease monitoring and strict criteria for resuming

Table 2. Key characteristics of selected clinical trials of discontinuation of TKIs

Reference	TKI/-treatment line	Median duration of TKI treatment	DMR status	Median duration of DMR	Trigger to restart TKI	Patients in TFR (%)
STIM [9••, 10] (*n* = 100)	Imatinib, first	50 months	UMRD for ≥2 years	35 months	Loss of UMRD	38 at 60 months
TWISTER [11, 12] (*n* = 40)	Imatinib, first	70 months	UMRD for ≥2 years	36 months	Loss of UMRD	45 at 60 months
STIM2 [13] (*n* = 218)	Imatinib, first	79 months	UMRD for ≥2 years	39 months	Loss of UMRD	50 at 24 months
DOMEST [14] (*n* = 99)	Imatinib, first	100 months	$MR^{4.0}$ for ≥2 years	55 months	Loss of $MR^{4.0}$	64 at 24 months
A-STIM [15•] (*n* = 80)	Imatinib, first	79 months	UMRD for ≥2 years	41 months	Loss of UMRD Loss of MMR	44 at 36 months 61 at 36 months
KID [16] (*n* = 90)	Imatinib, first	81 months	UMRD for ≥2 years	40 months	Loss of MMR	69 at 24 months
ISAV [17] (*n* = 108)	Imatinib, first	103 months	UMRD for ≥18 months	26 months	Loss of MMR	48 at 36 months
JALSG-STIM213 [18] (*n* = 68)	Imatinib, first	97 months	$MR^{4.0}$ for ≥2 years	67 months	Loss of MMR	65 at 36 months
EURO-SKI [19••] (*n* = 755)	Imatinib, first	7.5 years	$MR^{4.0}$ for ≥1 year	4.7 years	Loss of MMR	49 at 24 months
DESTINY [20, 21] (*n* = 125) (*n* = 49)	Imatinib, first	6.5 years 7.7 years	$MR^{4.0}$ for ≥1 year MMR for ≥1 year	NR 5.5 years	Loss of MMR Loss of MMR	72 at 36 months 36 at 36 months
DADI First-Line [22] (*n* = 58)	Dasatinib, first	40 months	$MR^{4.0}$ for ≥1 year	23 months	Loss of $MR^{4.0}$	55 at 12 months
DADI [23, 24] (*n* = 63)	Dasatinib, second	82 months	$MR^{4.0}$ for ≥1 year	NR	Loss of $MR^{4.0}$	44 at 36 months
D-STOP [25] (*n* = 54)	Dasatinib, first and second	92 months	$MR^{4.0}$ for ≥2 years	51 months	Loss of $MR^{4.0}$	63 at 12 months
DASFREE [26] (*n* = 84)	Dasatinib, first and second	69 months	$MR^{4.5}$ for ≥2 years	28 months	Loss of MMR	46 at 24 months
STOP 2G-TKI [27] (*n* = 30)	Dasatinib and Nilotinib, first and second	76 months	UMRD for ≥2 years	29 months	Loss of MMR	54 at 48 months
STAT2 [28] (*n* = 78)	Nilotinib, second	99 months	$MR^{4.5}$ for ≥2 years	51 months	Loss of $MR^{4.5}$	63 at 36 months

Table 2. (Continued)

Reference	TKI/-treatment line	Median duration of TKI treatment	DMR status	Median duration of DMR	Trigger to restart TKI	Patients in TFR (%)
ENESTop [29] (*n* = 126)	Nilotinib, second	88 months	$MR^{4.5}$ for ≥1 year	32 months	Loss of $MR^{4.0}$	53 at 24 months
ENESTfreedom [30, 31] (*n* = 190)	Nilotinib, first	44 months	$MR^{4.5}$ for ≥1 year	30 months	Loss of MMR	49 at 24 months

TKI tyrosine kinase inhibitor, *DMR* deep molecular response, *TFR* treatment-free remission, *UMRD* undetectable minimal residual disease, *MMR* major molecular response, *MR* molecular response

therapy were followed, CML sensitivity to TKI therapy was largely retained. Indeed, DMR could be restored soon after treatment reintroduction in more than 90% of the patients [32].

Predictors of successful TKI discontinuation

Despite promising results, the probability of a successful treatment interruption remains uncertain, which can be a cause of anxiety for both patients and clinicians. The exact mechanism of relapse after TKI discontinuation is unknown, even though several studies have described clinical and biologic predictive factors potentially associated with TFR success. These include age, sex, Sokal risk score, type of *BCR-ABL1* transcript, number and type of NK cells at the time of TKI discontinuation, duration of TKI treatment, prion interferon-alpha therapy, duration of DMR, and depth of response. Of these, the total duration of TKI treatment and the duration of DMR prior to TKI discontinuation emerged as the most strongly associated with a higher probability of TFR [9••, 16, 19••, 33, 34]. A consistent inclusion criterion in most clinical studies of TKI discontinuation was a minimum duration of therapy of 3 years and a sustained DMR of at least 1 year. Indeed, the TFR success rate of patients in stable MMR, but not in DMR, seems to be significantly lower than for stable DMR, but further TFR data are required for this group [35]. Indeed, a more stringent depth of molecular response prior to TKI discontinuation might be associated with a higher likelihood of successful TFR outcome [36, 37]. However, differences in clinical trial design and discrepancies in the classification of the level of molecular response between laboratories involved in clinical trials can result in a bias concerning the proportion of patients that can achieve TFR [37]. Thus, the results of the distribution of patients by molecular response level should be routinely published along TFR data, and such differences need to be considered when comparing results from different studies [37]. Furthermore, data from the EURO-SKI trial suggest that each additional year of DMR (defined as a molecular response of at least $MR^{4.0}$) under TKI treatment seems to be associated with an increase of 2–3% of remaining in MMR after treatment

discontinuation [19••]. Moreover, recent data seems to suggest that initial de-escalation of TKI therapy before discontinuation might improve the success of TFR. Indeed, de-escalation of TKI therapy to half the standard dose for a period of 12 months in patients in stable $MR^{4.0}$ before treatment interruption resulted in a subsequent 2-year molecular relapse-free survival of 72%, although the mechanism of its benefit is not yet clear [35]. However, to date, all these factors are still far from having a meaningful impact on clinical practice, and a validated TFR predictive algorithm has not yet been reported. Nevertheless, irrespective of the criteria used in a TFR attempt, there is a consensus that loss of MMR should be the trigger to restart treatment, since this surrogate marker has been validated in most studies [38]. Confirmation of MMR loss on a second evaluation is not required or advisable since it could delay treatment resumption [5••].

Requirements for TKI discontinuation

Treatment interruption is a safe procedure that should be performed only in centers with access to high-quality molecular monitoring and after careful patient selection [39]. However, not all patients are comfortable with the possibility of interrupting treatment, preferring to remain on therapy [36]. For this reason, a previous discussion with the patient about the information available on TFR is of particular importance [35]. Both European LeukemiaNet (ELN) and National Comprehensive Cancer Network (NCCN) have recently published guidelines for discontinuation of TKI therapy in CML [5••, 40]. According to ELN, TKI discontinuation should be considered only in motivated patients in first CP, when access to high-quality RT-qPCR (sensitivity of detection of at least $MR^{4,5}$) using the IS with rapid turn-around of PCR results is warranted and when patients agree to more frequent monitoring after stopping treatment (monthly for the first months, every 2 months for months 6–12, and every 3 months thereafter) [5••] (Fig. 1). Moreover, TKI discontinuation should only be considered in patients in first-line therapy or second-line if intolerance was the only reason to change TKI with no prior treatment failure [5••]. Patients should present typical e13a2 or e14a2 *BCR-ABL1* transcripts at diagnosis, which excludes patients with rare, atypical transcripts since their results cannot be expressed in the IS. Duration of TKI therapy should be 5 years or longer for first-generation TKI imatinib and can be reduced to 4 years if a 2G-TKI such as nilotinib or dasatinib is used, which is slightly superior to the minimum of 3 years TKI treatment suggested by NCCN [5••, 40]. Ideally, TKI discontinuation can be attempted in patients with DMR duration longer than 3 years if the patient is in sustained $MR^{4.0}$ (2 years according to the NCCN guidelines) or 2 years if $MR^{4.5}$, but this should not preclude selected patients in $MR^{4.0}$ for at least 2 years to stop therapy [5••]. Centers which propose treatment discontinuation should have a centralized or local standardized molecular laboratory capable of providing a report within 4 weeks to allow prompt resumption of TKI therapy in case of MMR loss. Patients who lost MMR should be followed monthly by molecular monitoring until MMR is re-achieved, and thereafter indefinitely every 3 months [40]. For those rare patients who fail to achieve MMR after 3 months of TKI resumption, *BCR-ABL1* kinase domain mutation should be performed, and monthly molecular monitoring should be continued for

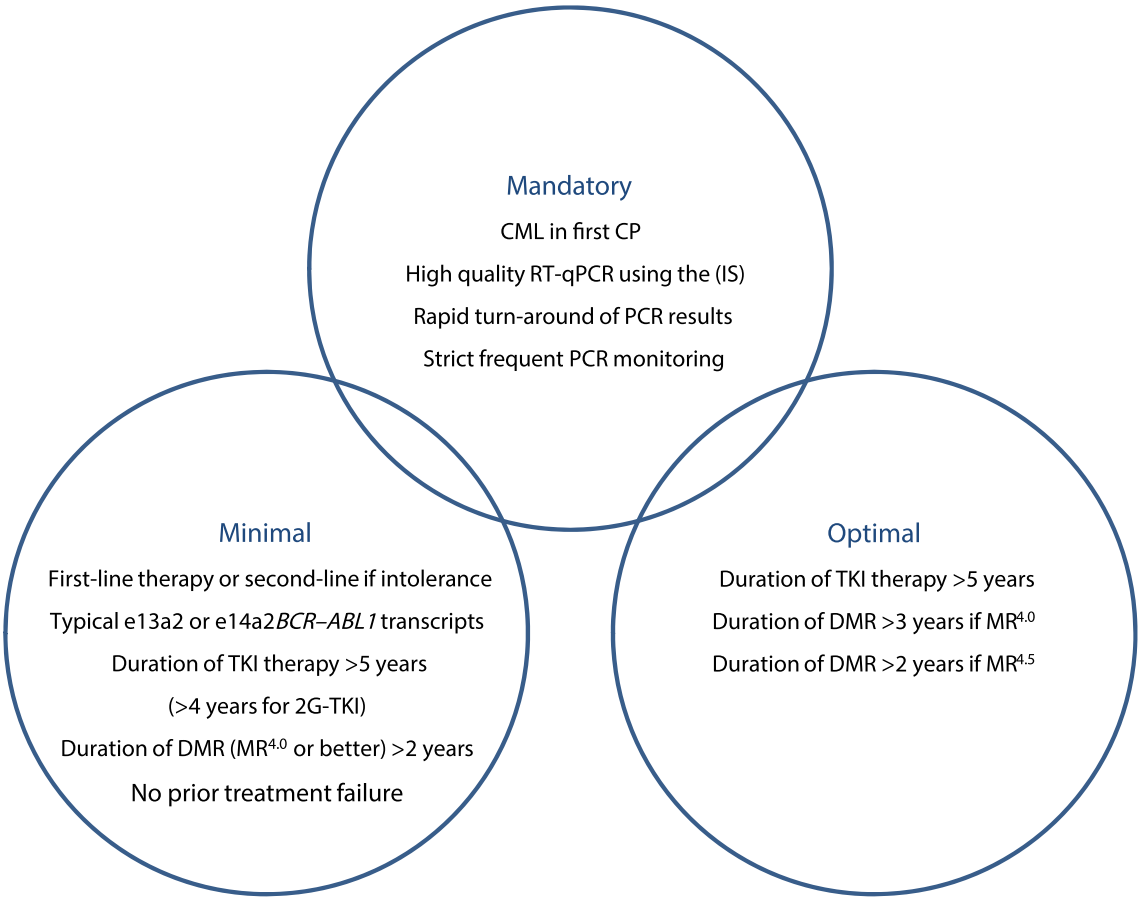

Fig. 1. Requirements for tyrosine kinase inhibitor discontinuation according to the ELN 2020 recommendations. *CML* chronic myeloid leukemia, *CP* chronic phase, *TKI* tyrosine kinase inhibitor, *DMR* deep molecular response

another 6 months [40]. Finally, considering the limitations of qRT-PCR, the implementation of even more sensitive and accurate methods, such as digital PCR, may provide more robust estimates of molecular response levels, allowing a better selection of patients for a TFR trial.

Second TFR attempt

A second attempt of TKI discontinuation after a first unsuccessful attempt is possible, although we still lack robust data to support this strategy, such as the identification of strong biomarkers that predict relapse. The largest study of TKI interruption after a first failed attempt was the French RE-STIM, in which 70 patients with molecular relapse after a first TKI discontinuation regained DMR and stopped treatment for a second time [41]. The probability of TFR at 36 months using loss of MMR as a trigger for treatment resumption with the same TKI was 35%; however, we must be cautious when interpreting these results since the criteria to restart TKI at the first attempt was loss of $MR^{4.5}$ [41]. In the Australasian CML8 study, 12 of the 22 patients who regained DMR, with undetectable disease after a first failed TKI interruption, attempted TKI

discontinuation for a second time [42]. In both attempts, loss of MMR was used as the definition of molecular relapse. With this criteria, half of the patients remained in MMR at a median follow-up of 8.6 years [42]. These results show that a second TKI discontinuation attempt is safe and that a first failed attempt does not preclude a second successful attempt. However, additional studies including prospective trials are clearly needed to address this question.

Treatment-free remission and pregnancy

All TKIs used to treat CML patients can have teratogenic effects as a result of their off-target activity, particularly when used during the first trimester of pregnancy [43–45]. Therefore, women with CML who wish to become pregnant are a specific population that needs TKI interruption before a pregnancy attempt or, if not possible, as soon as pregnancy is confirmed. According to published guidelines, women who are eligible for a TFR attempt can safely discontinue TKI treatment in order to conceive [5••, 40]. Subsequent management will depend on the maintenance or loss of MMR, and a plan for handling this eventuality should be previously discussed with the patient [5••]. It must be kept in mind that stopping TKI therapy too soon may increase the risk of disease recurrence that requires intervention. Nevertheless, women who lose MMR and are pregnant are likely to reach term without a clinical need for restarting treatment [5••]. Particularly challenging could be the case of the woman who desires to become pregnant, but that does not meet the minimum required criteria. In this case, substitution of TKI treatment by interferon could be an alternative [5••, 36]. For men taking TKIs, there is no associated increased risk of congenital abnormalities for the fetus and, therefore, men planning fatherhood do not need to discontinue treatment [43, 44].

Risks associated with TKI discontinuation

The safety of TKI discontinuation should be of the utmost importance since CML patients in DMR while receiving therapy have a negligible risk of secondary resistance, disease progression, or CML-related death. So far, of the more than 3000 patients who have been followed after TKI discontinuation, in only very rare instances, an adverse outcome was reported, but it is likely that numbers will increase with more patients observed over longer periods of time. One patient who lost MMR during the TFR phase was found to have a detectable nilotinib-resistant *BCR-ABL1* mutation (F359V), but whether this mutation was pre-existing could not be determined [46]. Three case reports describe the occurrence of a sudden blast crisis following a TFR attempt, which was lymphoid in two cases and myeloid in one case [15•, 47, 48]. In all three cases, the event occurred in patients who experienced molecular relapse following TKI discontinuation, resumed treatment, regained DMR, and had disease relapse 6–8.5 months after restarting TKI treatment [15•, 47, 48]. However, it is unknown if the events were triggered by the TFR attempt or whether they might have occurred even receiving continued treatment. After TKI interruption, most possible drug-related adverse events disappear; however, in approximately 30% of the patients, newly occurring or worsening of preexisting musculoskeletal pain can develop [49]. This is known as TKI withdrawal syndrome, can arise

within several weeks of TKI discontinuation and last up to several months, and is probably the result of TKI undefined off-target effects. Data from the EURO-SKI trial showed that longer treatment duration and the prior existence of musculoskeletal symptoms were associated with a higher incidence of withdrawal syndrome [19••]. In most patients, the symptoms are mild and self-limited, although some patients may require temporary treatment with anti-inflammatory drugs and in some instances with corticosteroids [5••].

Conclusion

Achieving TFR is currently the optimal therapy goal for patients with newly diagnosed CML. Good and structured communication between clinician and patient is a crucial step to maximize the probability of successful discontinuation of TKI therapy. The patient should be clearly aware that TFR is a safe strategy, unlikely to cause clinical relapse or disease progression. Candidate patients should be highly motivated and selected for TFR based on both their molecular response and the type and duration of TKI therapy. Only chronic-phase CML patients in first-line therapy, or second-line if intolerance was the only reason to change TKI, and who agree to a more frequent monitoring schedule after discontinuation should be selected. A sustained DMR (3 years for patients in $MR^{4.0}$ or 2 years if $MR^{4.5}$) is an essential prerequisite. Patients should be followed in an IS standardized molecular laboratory capable of providing a report within 4 weeks to allow prompt resumption of TKI therapy in case of molecular relapse. In the future, additional studies are warranted to identify novel biomarkers to more accurately select candidate patients for TFR.

Declarations

Conflict of Interest

Nuno Cerveira declares that he has no conflict of interest. Susana Bizarro declares that she has no conflict of interest. Manuel R. Teixeira declares that he has no conflict of interest. José M. Mariz declares that he has 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.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Deininger MW, Goldman JM, Melo JV. The molecular biology of chronic myeloid leukemia. Blood. 2000;96(10):3343–56.

2. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life

expectancy of the general population. J Clin Oncol. 2016;34(24):2851–7.
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(8):1648–71.
4. Cross NCP, White HE, Evans PAS, Hancock J, Copland M, Milojkovic D, et al. Consensus on BCR-ABL1 reporting in chronic myeloid leukaemia in the UK. Br J Haematol. 2018;182(6):777–88.
5.•• 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(4):966–8.

The 2020 update of the European Leukemia Net recommendations for the treatment, evaluation and follow-up of patients with CML.

6. Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med. 2003;349(15):1423–32.
7. Baccarani M, Castagnetti F, Gugliotta G, Rosti G, Soverini S, Albeer A, et al. The proportion of different BCR-ABL1 transcript types in chronic myeloid leukemia. An international overview. Leukemia. 2019;33(5):1173–83.
8. Rousselot P, Huguet F, Rea D, Legros L, Cayuela JM, Maarek O, et al. Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. Blood. 2007;109(1):58–60.
9.•• Mahon FX, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol. 2010;11(11):1029–3.

The first prospective trial for discontinuation TKI treatment which showed that 38% of selected CML patients could maintain a sustained molecular remission after treatment interruption.

10. 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;20(35):298–305.
11. Ross DM, Branford S, Seymour JF, Schwarer 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.
12. Ross DM, Pagani IS, Shanmuganathan N, Kok CH, Seymour JF, Mills AK, et al. Long-term treatment-free remission of chronic myeloid leukemia with falling levels of residual leukemic cells. Leukemia. 2018;32(12):2572–9.
13. Nicolini FE, Dulucq S, Boureau L, Cony-Makhoul P, Charbonnier A, Escoffre-Barbe M, et al. Evaluation of residual disease and TKI duration are critical predictive factors for molecular recurrence after stopping imatinib first-line in chronic phase CML patients. Clin Cancer Res. 2019;25(22):6606–13.
14. 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.
15.• 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):424–3.

A multicenter observational study that showed that loss of MMR was a practical and safe criterion for restarting therapy in patients with CML with prolonged CMR.

16. 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(6):717–23.
17. Mori S, Vagge E, le Coutre P, Abruzzese E, Martino B, Pungolino E, et al. Age and dPCR can predict relapse in CML patients who discontinued imatinib: the ISAV study. Am J Hematol. 2015;90(10):910–4.
18. Takahashi N, Tauchi T, Kitamura K, Miyamura K, Saburi Y, Hatta Y, et al. Deeper molecular response is a predictive factor for treatment-free remission after imatinib discontinuation in patients with chronic phase chronic myeloid leukemia: the JALSG-STIM213 study. Int J Hematol. 2018;107(2):185–93.
19.•• Saussele S, Richter J, Guilhot J, Gruber FX, Hjorth-Hansen H, Almeida A, et al. 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):747–5.

The largest clinical trial of TKI discontinuation in patients with CML that confirmed that patients with CML who have achieved deep molecular responses have good molecular relapse-free survival, particularly those who have been in deep molecular response for a long time.

20. Clark RE, Polydoros F, Apperley JF, Milojkovic D, Pocock C, et al. De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY): an interim analysis of a non-randomised, phase 2 trial. Lancet Haematol. 2017;4(7):e310–e16.
21. Clark RE, Polydoros F, Apperley JF, Milojkovic D, Rothwell K, Pocock C, et al. De-escalation of tyrosine kinase inhibitor therapy before complete treatment discontinuation in patients with chronic myeloid leukaemia (DESTINY): a non-randomised, phase 2 trial. Lancet Haematol. 2019;6(7):e375–e83.

22. Kimura S, Imagawa J, Murai K, Hino M, Kitawaki T, Okada M, et al. Treatment-free remission after first-line dasatinib discontinuation in patients with chronic myeloid leukaemia (first-line DADI trial): a single-arm, multicentre, phase 2 trial. Lancet Haematol. 2020;7(3):e218–e25.
23. 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.
24. Okada M, Imagawa J, Tanaka H, Nakamae H, Hino M, Murai K, et al. Final 3-year results of the dasatinib discontinuation trial in patients with chronic myeloid leukemia who received dasatinib as a second- line treatment. Clin Lymphoma Myeloma Leuk. 2018;18(5):353–60.
25. 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.
26. Shah NP, García-Gutiérrez V, Jiménez-Velasco A, Larson S, Saussele S, Rea D, et al. Dasatinib discontinuation in patients with chronic-phase chronic myeloid leukemia and stable deep molecular response: the DASFREE study. Leuk Lymphoma. 2020;61(3):650–9.
27. Rea D, Nicolini FE, Tulliez M, Guilhot F, Guilhot J, Guerci-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.
28. 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):1835–18.
29. 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.
30. 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.
31. Ross DM, Masszi T, Gómez Casares MT, Hellmann A, Stentoft J, Conneally E, et al. Durable treatment-free remission in patients with chronic myeloid leukemia in chronic phase following frontline nilotinib: 96-week update of the ENESTfreedom study. J Cancer Res Clin Oncol. 2018;144(5):945–54.
32. Dulucq S, Astrugue C, Etienne G, Mahon FX, Benard A. Risk of molecular recurrence after tyrosine kinase inhibitor discontinuation in chronic myeloid leukaemia patients: a systematic review of literature with a meta-analysis of studies over the last ten years. Br J Haematol. 2020;189(3):452–68.
33. 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 Dec;55(12):2879–86.
34. Cerveira N, Loureiro B, Bizarro S, Correia C, Torres L, Lisboa S, et al. Discontinuation of tyrosine kinase inhibitors in CML patients in real-world clinical practice at a single institution. BMC Cancer. 2018;18(1):1245.
35. Clark RE, Polydoros F, Apperley JF, Milojkovic D, Rothwell K, Pocock C, et al. De-escalation of tyrosine kinase inhibitor therapy before complete treatment discontinuation in patients with chronic myeloid leukaemia (DESTINY): a non-randomised, phase 2 trial. Lancet Haematol. 2019;6(7):e375–e83.
36. Ross DM, Hughes TP. Treatment-free remission in patients with chronic myeloid leukaemia. Nat Rev Clin Oncol. 2020;17(8):493–503.
37. Cerveira N, Diamond J, Matos S, Amorim ML, Coucelo M, Bizarro S, et al. Negative MR4·0 chronic myeloid leukaemia and its possible implications for treatment-free remission. Br J Haematol. 2019;186(6):e181–e4.
38. 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.
39. Almeida A, Pierdomenico F, Guerrero BP, Saraiva S, Montalvão A, Coutinho J, et al. Recommendations from a Portuguese expert group for discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia patients in clinical practice. Acta Medica Port. 2019;32(7-8):550–7.
40. National Comprehensive Cancer Network (2018) Chronic Myeloid Leukemia (Version 2.2021). https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed 2021-04-02.
41. Legros L, Nicolini FE, Etienne G, Rousselot P, Rea D, Giraudier S, et al. Second tyrosine kinase inhibitor discontinuation attempt in patients with chronic myeloid leukemia. Cancer. 2017;123(22):4403–10.
42. Ross DM, Pagani IS, Shanmuganathan N, Kok CH, Seymour JF, Mills AK, et al. Long-term treatment-free remission of chronic myeloid leukemia with falling levels of residual leukemic cells. Leukemia. 2018;32(12):2572–9.
43. Pye SM, Cortes J, Ault P, Hatfield A, Kantarjian H, Pilot P, et al. The effects of imatinib on pregnancy outcome. Blood. 2008;111(12):5505–8.

44. Cortes JE, Abruzzese E, Chelysheva E, Guha M, Wallis N, Apperley JF. The impact of dasatinib on pregnancy outcomes. Am J Hematol. 2015;90(12):1111–5.
45. Cerveira N, Almeida A. Evidence-based criteria for tyrosine kinase inhibitor interruption in pregnancy. J Clin Oncol. 2019;37(1):89–90.
46. 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.
47. Papalexandri A, Saloum R, Touloumenidou T, Papathanasiou M, Lalayanni C, Baldoumi E, et al. Blast crisis of CML after TKI discontinuation in a patient with previous stable deep molecular response: is it safe to stop? Hemasphere. 2018;2(6):e157.
48. Rea R, Nicolini FE, Tulliez M, Rousselot P, Gardembas M, Etienne G, et al. Prognostication of molecular relapses after dasatinib or nilotinib discontinuation in chronic myeloid leukemia (CML): A FI-LMC STOP 2G-TKI Study Update. Blood. 2019;134:30.
49. Richter J, Soderlund S, Lubking A, Dreimane A, Lotfi K, Markevarn B, et al. Musculoskeletal pain in patients with chronic myeloid leukemia after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome? J Clin Oncol. 2014;32:2821–3.

Publisher's note