Original Article

Discontinuation of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia: Recommendations for Clinical Practice From the French Chronic Myeloid Leukemia Study Group

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BACKGROUND: The ultimate goal of chronic myeloid leukemia management in the tyrosine kinase inhibitor (TKI) era for patients who obtain deep molecular responses is maintaining a durable off-treatment response after treatment discontinuation; this situation is called treatment-free remission (TFR). Knowledge accumulated during the last 10 years justifies moving TFR strategies from research to clinical practice. **METHODS:** Twenty experts from the French Chronic Myeloid Leukemia Study Group (France Intergroupe des Leucémies Myéloïdes Chroniques), including 17 hematologists, 2 molecular biologists, and 1 cytogeneticist, critically reviewed published data with the goal of developing evidence-based recommendations for TKI discontinuation in clinical practice. **RESULTS:** Clinically relevant questions were addressed, including the selection of candidate patients (with known prognostic factors for outcomes taken into account), detailed monitoring procedures during the treatment-free phase, a definition of relapse requiring therapy resumption, and monitoring after treatment reintroduction. **CONCLUSIONS:** This work presents consensus statements with the aim of guiding physicians and biologists by means of pragmatic recommendations for safe TKI discontinuation in daily practice. ***Cancer* 2018;000:000–000.** *© 2018 American Cancer Society.*

KEYWORDS: chronic myeloid leukemia, clinical practice, recommendations, treatment discontinuation, tyrosine kinase inhibitors.

INTRODUCTION

Adenosine triphosphate–competitive tyrosine kinase inhibitors (TKIs) targeting BCR-ABL1, the driving oncoprotein of chronic myeloid leukemia (CML), revolutionized patient outcomes. After the introduction of imatinib in the early 2000s, the more potent second-generation drugs dasatinib, nilotinib, and bosutinib, followed by the third-generation compound ponatinib, enriched the therapeutic arsenal.[1] Until recently, obtaining a major molecular response (MMR; *BCR-ABL1*/control gene internationally standardized [IS] ratio $\leq 0.1\%$) was considered to be the gold standard for maximum clinical benefit. Indeed, adult patients with chronic-phase CML who achieve and maintain an MMR can expect very long progression-free survival and a nearly normal life expectancy as long as they receive lifelong treatment.[2] The impact of comorbidities on overall survival in such patients is even greater than the impact of CML itself.[3,4]

However, evidence showing that TKIs are unable to kill quiescent leukemic stem cells (LSCs), that *BCR-ABL1* transcripts remain detectable in most patients, and that those in whom *BCR-ABL1* transcripts become undetectable with highly sensitive polymerase chain reaction techniques continue to carry leukemic DNA led to the recommendation that patients stay on treatment forever.[5,6] Fundamental research is aimed at understanding the mechanisms of LSC persistence and finding approaches for LSC eradication, but results have not yet been successfully translated into the clinic.[6] Nevertheless, the concept of indefinite TKI treatment for all patients was called into question when results from the STop IMatinib (STIM) and TWISTER trials, which involved patients with "molecularly undetectable disease" for prolonged period of times on imatinib, challenged the statement that TKIs should never be stopped.[7,8] Since then, multiple other imatinib and second-generation TKI discontinuation studies have been conducted. All have confirmed that approximately 50% of patients with a deep molecular response (DMR) for several years, such as molecular response 4 (MR4; *BCR-ABL1* IS

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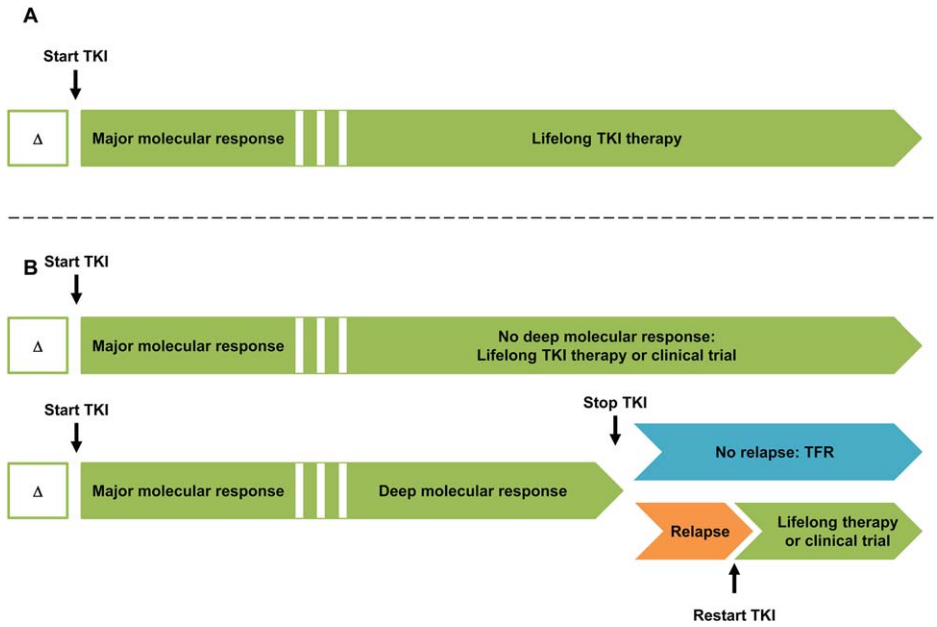

Figure 1. Changing paradigm in CML management. (A) The classic treatment goal for CML patients consists of the achievement of a major molecular response to confer maximum protection from disease resistance or progression to blast crisis and maintenance of TKI therapy indefinitely. (B) The discovery that patients with a long TKI treatment duration and a sustained deep molecular response can successfully stop therapy in approximately 50% of cases is currently leading to the integration of TKI discontinuation into CML management schemes. Δ indicates chronic-phase chronic myeloid leukemia at diagnosis; CML, chronic myeloid leukemia; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

ratio $\leq$ 0.01% or undetectable *BCR-ABL1* with at least 10,000 copies of *ABL1*) or molecular response 4.5 (MR4.5; *BCR-ABL1* IS ratio $\leq$ 0.0032% or undetectable *BCR-ABL1* with at least 32000 copies of *ABL1*), can successfully stop TKIs; this situation is called treatment-free remission (TFR).[9-11] Importantly, these studies have demonstrated that with careful monitoring, CML-related deaths do not occur, and molecular relapses caused by the outgrowth of residual leukemic cells are sensitive to TKI resumption.

TFR becomes an increasingly important consideration in the real-life setting and, traditional recommendations to pursue treatment lifelong in all patients, such as those provided by the National Comprehensive Cancer Network (NCCN), have been recently modified (https://www.nccn.org/; Fig. 1). Although clinical trials and fundamental research are needed to optimize TKI discontinuation strategies, we must recognize that TKI discontinuation has become a reality in clinical practice. Our goal was to develop recommendations based on the pioneering experience of the French Chronic Myeloid Leukemia Study Group (France Intergroupe des Leucémies Myéloïdes Chroniques) and on a comprehensive and critical review of knowledge accumulated to date.

PATIENT SELECTION FOR TKI DISCONTINUATION

Our recommendations for patient selection are intended to provide a strategy offering the greatest possible TFR rates (Table 1). They apply exclusively to patients in chronic phase at diagnosis who are at least 18 years old at the time of TKI discontinuation.[12] Age has not emerged as an influence on molecular relapse in TKI discontinuation studies performed in adults. Although a long-lasting TKI treatment in childhood CML raises specific issues such as growth and endocrine disturbances, we feel that TKI discontinuation in children must not be attempted outside experienced pediatric centers. The reason for not including children in our recommendations relies on the fact that childhood CML differs in several ways from adult CML. First, pediatric CML is considered to be clinically and biologically more aggressive than adult CML.[13] Second, the incidence of CML in pediatric populations is approximately 10 times lower than that in adults, so data on TKI discontinuation in children are scarce.[14] Third, whether TKI discontinuation in children is as safe and successful as it is in adults needs to be investigated.

With respect to the impact of chronic-phase CML prognostic scores on first-line TKI discontinuation

TABLE 1. Patient Selection

Parameter	Criteria
Age	≥18 y old at TKI discontinuation
CML phase	CP only
Prognostic score at diagnosis	Not taken into account
Karyotype at diagnosis	Not taken into account
BCR-ABL1 transcripts	e13a2, e14a2, or e13a2 + e14a2
TKI treatment duration	≥5 y
Type of DMR	MR4.5 at least
DMR duration	≥2 y[a]
Prior treatment history	No allogeneic HSCT, progression, resistance, suboptimal response, or warning

Abbreviations: CML, chronic myeloid leukemia; CP, chronic phase; DMR, deep molecular response; HSCT, hematopoietic stem cell transplantation; MR4, molecular response 4; MR4.5, molecular response 4.5; RT-qPCR, real-time quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor.
[a] MR4.5 is confirmed in ≥4 consecutive tests. Because of known limits to RT-qPCR precision, at most 1 of the 4 assessments showing an MR4 is accepted.

outcomes, post hoc analyses in clinical trials have yielded inconsistent results. In STIM, patients with low or intermediate Sokal scores had significantly higher chances of remaining imatinib-free than patients with a high Sokal score.[15] In ENESTfreedom, a first-line nilotinib cessation trial, the lowest TFR rates were observed in patients with a high Sokal score at diagnosis.[16] In contrast, no obvious effect of the Sokal score was found in other trials such as KID, TWISTER, and JALSG-STIM213.[8,17,18] Thus, we did not include prognostic scores at diagnosis among the selection criteria for TKI discontinuation in clinical practice.

An important point to consider for patient selection is the type of *BCR-ABL1* transcripts. The majority of patients harbor major-type *BCR-ABL1*, namely e13a2, e14a2, or both, but in rare cases, minor transcripts can be found.[19] The characterization of transcripts is important because the use of inadequate primers or probes may lead to incorrect quantification or false-negative results by real-time quantitative polymerase chain reaction (RT-qPCR). Moreover, standardized definitions of molecular responses and scoring of DMR apply to major-type *BCR-ABL1* transcripts only.[20,21] Thus, the current recommendations do not apply to patients who have rare transcripts or whose transcripts have not been fully typed with appropriate techniques. Such patients should be referred for advice to experienced clinical and molecular biology centers.

Data from TKI discontinuation studies suggest that the duration of exposure to TKIs before therapy discontinuation and the DMR duration may be the most important modifiable prognostic outcome factors. We provisionally recommend at least 5 years of TKI treatment and at least 2 years of MR4.5 confirmed in at least 4 consecutive tests 6 months apart before TKI discontinuation is considered. These recommendations are comparable to those provided in the European Society for Medical Oncology guidelines for CML.[22] Shorter durations of treatment or DMR do not exclude successful TKI discontinuation but are likely to decrease the chances for remaining treatment-free. In STIM, at least 3 years of imatinib was required for inclusion, with at least 2 years of nondetectability of *BCR-ABL1* transcripts with RT-qPCR techniques of at least 4.5-log sensitivity.[7] It appeared that patients who received at least 54 months of imatinib had a significantly lower risk of molecular relapse than patients with shorter therapy durations.[15] In EURO-SKI, a minimum duration of 3 years of TKI treatment was required for inclusion, including at least 1 year of MR4. A threshold of at least 5.8 years of imatinib and 3.1 years of MR4 identified patients with the lowest molecular relapse probabilities, but the latter cutoff was the most important.[23] Whether treatment and DMR duration also play roles in stopping first-line dasatinib or nilotinib in patients has not been investigated yet.

The question of which level of DMR, namely MR4 or MR4.5, is best for TKI discontinuation is an important one. In JALSG-STM213, patients in MR4.5 with undetectable *BCR-ABL1* transcripts just before imatinib discontinuation had significantly higher TFR probabilities than those in MR4.5 but with detectable residual disease.[18] In ENESTfreedom, patients constantly in MR4.5 the year before nilotinib cessation had a greater chance to remain nilotinib-free than patients in whom *BCR-ABL1* fluctuated between MR4 and MR4.5.[16] In EURO-SKI, whether *BCR-ABL1* transcripts were detectable or not at the time of imatinib discontinuation did not seem to influence TFR rates.[24] Thus, although one intuitively expects that the lowest residual disease levels may be associated with the best TFR rates, no clear-cut answer has been provided to date. RT-qPCR has intrinsic limitations, such as relatively poor precision, especially at low levels of residual disease, and variations in sensitivity from one test to another.[20] In addition, laboratories that have not maximized their lower limit of detection for *BCR-ABL1* transcripts may not be able to score at least MR4.5. In the future, the use of technologies with better quantitative accuracy than RT-qPCR, such as digital polymerase chain reaction, may help to answer which DMR level is most important for TKI discontinuation.[25]

It is important to note that in the DADI and STOP 2G-TKI studies, a DMR obtained upon salvage therapy with dasatinib or nilotinib after imatinib resistance or a

suboptimal response conferred significantly lower chances of successfully discontinuing second-generation TKIs than when they were given in the first- or second-line setting because of prior TKI intolerance.[26,27] In the second-line nilotinib discontinuation study ENESTop, no difference in TFR rates between patients with prior imatinib intolerance and patients with resistance was found.[28] The ongoing LAST trial, designed to evaluate imatinib, dasatinib, nilotinib, or bosutinib discontinuation, excludes patients with a history of resistance but not patients who have been suboptimal responders to a prior treatment (NCT02269267). TFR data for patients who did not obtain an MMR or DMR on imatinib and who switched to nilotinib in the ENESTpath trial are pending (NCT01743989). Thus, we feel that at this point, TKI discontinuation in patients with a history of resistance or suboptimal responses should remain in the clinical research domain.[29] Apart from these specific situations, we found no robust reason to distinguish imatinib-treated patients and new-generation TKI–treated patients, as in the NCCN guidelines for TKI discontinuation in CML (version 2.2017), although no trial has addressed the feasibility of ponatinib discontinuation yet.

DEFINITION OF MOLECULAR RELAPSE AFTER TKI DISCONTINUATION

Defining relapse after TKI discontinuation is critical because it is a trigger for rapid treatment re-introduction and it has a direct impact on the TKI discontinuation success rate. On one hand, a too restrictive relapse definition may lead to unnecessary TKI prescriptions in some patients who in fact do not require retreatment. On the other hand, waiting for the leukemic burden to become too high may jeopardize outcomes because we cannot exclude that, on account of the genetic instability of CML cells, resistance to TKIs or progression may emerge.

There have been differences in molecular relapse definitions across TKI discontinuation trials, which have ranged from detectable *BCR-ABL1* transcripts at any value to MMR loss. In STIM, molecular relapse was defined as detectability of *BCR-ABL1* transcripts in 2 consecutive samples with a rise between the 2 samples or MMR loss in any single sample.[7] The reluctance of some patients to rapidly restart therapy led to the discovery that the detection of *BCR-ABL1* transcripts at low levels after imatinib discontinuation did not automatically lead to CML relapse.[7,30] The A-STIM study validated MMR loss as a trigger for restarting therapy.[31] Other imatinib or second-generation TKI discontinuation studies, such as ISAV, KID, EURO-SKI, JALSG-STIM213, ENESTfreedom, STOP 2G-TKI, and DASFREE, adopted MMR loss to define molecular relapse.[17,18,23,27,32-34] In these trials, major concerns after rapid TKI resumption due to MMR loss were exceptional, and the NCCN adopted MMR loss as a signal for promptly resuming TKI therapy in its guideline for TKI discontinuation in CML (version 2.2017). Notably, none of the TKI discontinuation trials performed to date have allowed patients to remain treatment-free above the threshold of a 0.1% IS ratio because upon MMR loss, a cytogenetic relapse followed by a hematologic relapse is expected to occur on account of the rapid growth kinetics of leukemic cells.[35] Thus, despite intrinsic RT-qPCR assay variation, we recommend the loss of MMR on a single occasion as the definition of relapse and the criterion for treatment resumption.

PATIENT INFORMATION BEFORE TKI DISCONTINUATION

Safe TKI discontinuation relies not only on physicians and biologists but also on patients. Written information on the estimated risk of molecular recurrence of CML, on the need for frequent monitoring at least during the first year, and on the importance of restarting treatment in case of molecular relapse may be provided. Compliance with monitoring and retreatment rules is absolutely necessary. A patient's decision not to stop therapy despite fulfilling the requirements for TKI discontinuation in clinical practice should be respected.

CLINICAL AND BIOLOGICAL SURVEILLANCE DURING THE TKI-FREE PERIOD

Clinical Surveillance

After TKI discontinuation, we recommend clinical visits quarterly during the first year and every 3 to 6 months thereafter (Table 2). Although molecular relapses are asymptomatic in the absence of a hematologic relapse and CML progression has rarely been reported after TKI discontinuation, the detection of any unexpected warning signs that may be directly related to CML is important. Clinical visits also provide the opportunity to address patient concerns (especially a fear of losing CML control), discuss RT-qPCR results, check for the disappearance of TKI-related side effects, and adjust monitoring tests and schedules whenever necessary. The onset of a TKI withdrawal syndrome consisting of newly occurring or worsening osteoarticular pain has been described in approximately one-third of patients stopping therapy.[36] It occurs within 1 to 2 months after treatment cessation, it is usually benign and transient, and a course of nonopioid

TABLE 2. Monitoring During the Treatment-Free Phase

Parameter	Frequency
Physical examination	Quarterly during year 1 and then every 3 to 6 mo
CBC and peripheral blood RT-qPCR	Monthly during the first 6 mo, every 2 mo from 7 to 12 mo, quarterly during the second year, and then every 3 to 6 mo
Bone marrow cytology and karyotype	Not required
Mutation analyses	Not required
Biochemistry	Fasting glucose and HbA_{1c} in diabetic patients 3 to 6 mo after nilotinib discontinuation Lipid profile 3 to 6 mo after TKI discontinuation if treatment with statins TSH 6 wk to 3 mo after TKI discontinuation in case of levothyroxine therapy Other tests at the discretion of the treating physician
Coagulation tests	Frequent INR assessments shortly after TKI discontinuation in patients on warfarin or fluindione

Abbreviations: CBC, complete blood count; HbA_{1c}, hemoglobin A_{1c}; INR, international normalized ratio; RT-qPCR, real-time quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor; TSH, thyroid-stimulating hormone.

analgesics or nonsteroidal anti-inflammatory drugs may be needed until resolution. In cases of severe or unexpectedly prolonged pain, a multidisciplinary management approach involving rheumatologists may be needed to rule out differential diagnoses. The mechanism of this phenomenon is unknown, and whether tapering TKI doses before discontinuation may decrease its frequency or intensity has not been evaluated. Finally, patients should be regularly reminded of the importance of monitoring because we cannot exclude the possibility that adherence to surveillance may decline over months or years after TKI discontinuation.

Hematological Monitoring

Hematological monitoring should be performed in standardized laboratories according to the European LeukemiaNet recommendations for *BCR-ABL1* messenger RNA quantification by RT-qPCR and for the scoring of DMR.[20,21] Results should be made available to treating physicians rapidly, within 2 to 3 weeks. To satisfy this requirement, molecular biologists should be informed of TKI discontinuation attempts in individual patients. During the treatment-free period, we recommend monthly RT-qPCR tests together with complete blood counts for the first 6 months, then every 2 months until month 12, and then every 3 to 6 months for patients remaining in MR4.5 and every 3 months otherwise (Table 2). Indeed, the majority of molecular relapses occur within 6 to 12 months, and the transition from a DMR to MMR loss may be abrupt. Early relapses are characterized by an exponential increase in *BCR-ABL1* (rising by 0.5-1 log per month), whereas later relapses usually have slower kinetics.[8,9,30] Nevertheless, we recognize that slightly less frequent monitoring during the first year may not substantially affect outcomes.[37] How often tests should be performed in patients who remain treatment-free in the long term is an open question because surveillance data beyond 3 to 5 years are limited. The frequency may be adapted to the individual patient's residual disease level and evolution pattern. Updated results of the STIM study were recently published with a median follow-up after imatinib discontinuation of 77 months, and no molecular relapses were seen after 22 months.[15] Very long-term follow-up data (>5 years) from studies using MMR loss as a definition of molecular relapse are not available yet. One should keep in mind that few very late relapses (>5 years) have been reported after myeloablative allogeneic hematopoietic stem cell transplantation for CML in the first chronic phase.[38] Thus, we recommend lifelong monitoring of *BCR-ABL1* during the treatment-free phase because relapses after very long latent periods may be seen.

Other Biological Evaluations

Besides RT-qPCR, there may be a need for vigilance in other biological parameters that can be modified upon TKI discontinuation (Table 2). Surveillance of fasting glucose and glycosylated hemoglobin may be proposed to diabetic patients 3 to 6 months after the discontinuation of nilotinib because of the capacity of this drug to modify glycemic control.[39] In patients on lipid-lowering agents, cholesterol may be verified 3 to 6 months after TKI discontinuation because TKIs interfere with most statin metabolism through cytochrome P450 3A4 inhibition.[39] In hypothyroid patients, T4 and thyroid-stimulating hormone levels may be checked after 6 to 12 weeks to detect any variation that would require levothyroxine dose adjustments.[39] Special attention should be given to patients taking anticoagulants such as fluindione or warfarin, and we recommend frequent monitoring of international normalized ratio values during the first few weeks after TKI cessation.

MANAGEMENT OF RELAPSES AFTER TKI DISCONTINUATION

Our recommendations for the management of relapses are summarized in Table 3. The loss of an MMR on a

TABLE 3. Monitoring of Relapsing Patients

Time Point	Parameter
TKI resumption visit	Physical examination CBC, biochemistry Pregnancy test[a] Bone marrow cytology, karyotype, and *BCR-ABL1* mutation analysis only in case of an unexpected event such as a loss of a complete hematologic response
Quarterly during the first year after TKI re-introduction or until re-achievement of MMR/DMR and then every 3 to 6 mo	CBC, biochemistry RT-qPCR
Every 3 to 6 mo beyond the first year	CBC, biochemistry RT-qPCR
In the absence of MMR recovery within 6 to 12 mo	*BCR-ABL1* mutation analysis

Abbreviations: CBC, complete blood count; DMR, deep molecular response; MMR, major molecular response; RT-qPCR, real-time quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor
[a] For women with child-bearing potential.

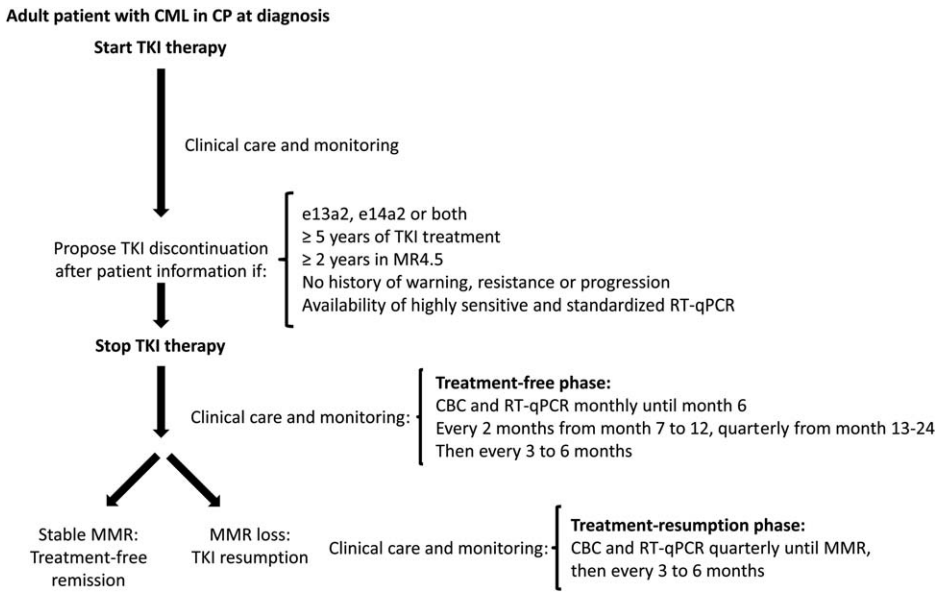

Figure 2. Overview of the recommendations of the French Chronic Myeloid Leukemia Study Group (France Intergroupe des Leucémies Myéloïdes Chroniques) for TKI discontinuation in clinical practice. CBC indicates complete blood count; CML, chronic myeloid leukemia; CP, chronic phase; MMR, major molecular response; MR4.5, molecular response 4.5; RT-qPCR, real-time quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor.

single occasion is an indication to restart TKIs with a maximum delay of 1 month. The same TKIs used before discontinuation may be chosen unless the patient previously faced significant tolerance issues. In women of child-bearing age, a pregnancy test should be proposed before TKI resumption because of the risk of fetal malformation.[40] After TKI resumption, we recommend monitoring *BCR-ABL1* transcripts every 3 months until an MMR and a DMR are regained and then every 3 to 6 months; this is consistent with the frequency of monitoring recommended by the European LeukemiaNet.[5] Notably, the speed of response may vary from one patient to another and may depend on several factors, including the *BCR-ABL1* transcript level at relapse, the type of TKI, and the dose at which it has been reintroduced. In parallel to response monitoring, physicians should be vigilant about TKI tolerability, especially with new-generation drugs. Whether retreatment should be continued lifelong or there is hope for a second successful TKI discontinuation episode is currently under investigation, and multiple TKI discontinuation attempts or add-on therapies are not recommended outside clinical studies.[41]

In the absence of MMR recovery within 3 to 6 months despite a well-conducted TKI rechallenge, screening for *BCR-ABL1* mutations should be performed, and treatment should be promptly modified, with the presence and type of the *BCR-ABL1* mutation taken into account. In TKI discontinuation trials, almost all patients who lost an MMR were sensitive to TKI rechallenge. In EURO-SKI, an MMR was regained after a median time of 3

months after imatinib resumption.[23] In STOP 2G-TKI, an MMR was regained by all patients after a median time of 2 months after dasatinib or nilotinib reintroduction.[27] It is important to bear in mind that notable exceptions to these favorable scenarios do exist. In ENESTfreedom, 98.8% of relapsing patients rapidly regained an MMR upon nilotinib resumption. However, an F359V BCR-ABL1 kinase domain mutation was detected in 1 patient not responding to nilotinib.[32] In A-STIM, 1 patient progressed to a lymphoid blast phase after imatinib resumption.[31] Progression occurred after an MMR was regained, so this situation is being considered a "sudden blast crisis" that may exceptionally be seen in optimal responders.[42] Determining the exact frequency of such catastrophic medical events will be a key issue in the real-life setting, and we encourage the creation of national or international centralized reporting systems.

CONCLUSION AND PERSPECTIVE

Multiple studies have demonstrated that TKI cessation is feasible and safe in CML patients with a durable DMR on therapy, and the concept of lifelong treatment for all patients is no longer valid. In our recommendations for TKI discontinuation in clinical practice, we made the choice to take into account known prognostic factors for successful TFR for patient selection to guide physicians, biologists, and thus patients (Fig. 2). However, we recognize that some questions remain unanswered, some points may be brought into debate, and revisions may be needed in the future because of new knowledge. Clinical trials are still needed to solve pending issues as well as biological investigations aimed at developing approaches to expanding TKI discontinuation opportunities and better controlling LSCs with the idea of curing the disease.

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AUTHOR CONTRIBUTIONS

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