REGULAR ARTICLE

blood advances

Treatment-free remission in patients with chronic myeloid leukemia: recommendations of the LALNET expert panel

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Key Points

- Discontinuing TKIs in LA is the new goal, and LALNET TFR recommendations for CML patients are an unmet need.
- TFR recommendations adapted to LA needs will make discontinuation feasible and safe in real life in the region.

Tyrosine kinase inhibitors (TKIs) have dramatically changed the survival of chronic myeloid leukemia (CML) patients, and treatment-free remission (TFR) has recently emerged as a new goal of CML treatment. The aim of this work was to develop recommendations for TKI discontinuation in Latin America (LA), outside of clinical trials. A working group of CML experts from LA discussed 22 questions regarding TFR and reached a consensus for TFR recommendations in the region. TFR is indicated in patients in first chronic phase, with typical BCR-ABL transcripts, under TKI treatment of a minimum of 5 years, in sustained deep molecular response (DMR; molecular response 4.5 [MR4.5]) for 2 years. Sustained DMR must be demonstrated on at least 4 international reporting scale quantitative polymerase chain reaction (PCR) tests, separated by at least 3 months, in the immediate prior 2 years. After second-line therapy, TFR is indicated in previously intolerant, not resistant, patients. Molecular monitoring is recommended monthly for the first 6 months, every 2 to 3 months from months 7 to 12, and every 3 months during the second year, indefinitely. Treatment should be reintroduced if major molecular response is lost. Monitoring of withdrawal syndrome, glucose levels, and lipid profile is recommended after discontinuation. After TKI reintroduction, molecular monitoring is indicated every 2 to 3 months until MR4.0 achievement; later, every 3 to 6 months. For the TFR attempt, having standardized and reliable BCR-ABL PCR tests is mandatory. These recommendations will be useful for safe discontinuation in daily practice and will benefit patients who wish to stop treatment in emergent regions, in particular, with TKI-related chronic adverse events.

Introduction

The recognition of the BCR-ABL oncoprotein as the constitutively active tyrosine kinase responsible for the development of chronic myeloid leukemia (CML) prompted the development of tyrosine kinase inhibitors (TKIs). These molecules have radically changed the clinical course of CML for most patients, turning

Submitted 31 August 2020; accepted 22 March 2021; prepublished online on *Blood Advances* First Edition 26 August 2021; final version published online 24 November 2021. DOI 10.1182/bloodadvances.2020003235.

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it from a fatal leukemia to a chronic disorder. Today, individuals with an optimal response may have a life expectancy close to that of the general population.[1-3] Despite the favorable outcome with current therapies, TKIs do not eradicate the CML stem cells. Because of this, the treatment recommendations, until recently, were to continue therapy indefinitely for all patients. The prolonged use of TKIs is associated with clinically relevant adverse events (AEs), such as cardiovascular events, pleural effusions, fatigue, muscular pain, and the possible increase in the incidence of second cancers.[4-7] When present, these AEs jeopardize quality of life. The high cost of indefinite TKI treatment has become a burden to the health care system and patients all over the world. That is especially relevant in low-middle income countries in Latin America (LA).

Recent studies have shown that TKI treatment can be safely discontinued in a selected group of chronic-phase (CP) CML patients who achieve deep molecular response (DMR), making treatment-free remission (TFR) a new goal of therapy.[8-13] TFR was first investigated in the TWISTER[13] and STIM1 trials.[8] The latter showed that the 41% who had achieved sustained complete molecular response (CMR) on quantitative polymerase chain reaction (qPCR) after long-term treatment with imatinib, continued in CMR after 1 year of TKI discontinuation.[8] Several other studies have confirmed the results with imatinib and provided similar data after discontinuation of nilotinib or dasatinib.[14] EURO-SKI, the largest discontinuation trial, demonstrated that ~50% of patients can persist without molecular relapse at 2 years.[15] Discontinuation trials are ongoing in LA, and have shown feasibility and similar outcomes in preliminary reports.[16,17]

The recent European Leukemia Net (ELN) recommendations (2020 version)[18] as well as the National Comprehensive Cancer Network (NCCN) guidelines[19] consider TKI discontinuation feasible in selected patients. European Society for Medical Oncology (ESMO) guidelines also include recommendations for TFR, especially focusing on the institutional and patient requirements for a safe TFR.[20]

LA is a vast and heterogenous region where the application of some advances in hematology practice is challenging. Public health policies are different among the various countries, but they all share many of the same limitations for care, usually related to health care access barriers and limited resources. During the last decade, cooperative efforts in LA have successfully organized a harmonization platform for BCR-ABL1 measurement (www.ph-is.com) with the participation of 30 LA laboratoriess from 10 different Latin American (LATAM) countries. To have an immediate clinical benefit on molecular response monitoring for patients in low-resource regions, this platform identified existing flaws in BCR-ABL quantification and brought up several technical recommendations to improve comparability between laboratories.[21]

The strict and more frequent monitoring, as recommended to make TFR feasible, has not yet been recognized by all government health authorities and insurance companies in LA countries. Various LA countries have local cooperative working groups with special interest in CML management but no regional collaborative approach in TFR local recommendations has been developed until now. As there are still many unanswered questions concerning TFR, the need for local TFR management guidelines in LA to conduct this strategy, outside of clinical trials, was identified as a priority to discuss in recent LA Leukemia Net (LALNET) meetings. Careful patient selection and optimal monitoring must be assured if TFR is to be considered a safe decision for the LA CML population. It is the hope of all participants that this collective effort might help better educate patients and physicians in the region about this approach and create awareness in health care authorities and third-party payers about not only the potential benefits that TFR carries, but also the risks if not properly implemented by those with shared responsibilities in the process.

Methods

A working meeting was held on 29 March 2019 at FUNDALEU (Buenos Aires, Argentina) to discuss TFR and its reality and impact in our region with CML experts and representatives from Argentina, Brazil, Chile, Colombia, Mexico, Peru, and Uruguay. A questionnaire addressing the various aspects of TFR was sent to all participants before the meeting. Responses were reviewed and discussed. Each CML expert answered 22 questions related to optimal criteria for TKI discontinuation, molecular monitoring, and other clinical aspects. During the event, opinions were harmonized and a consensus was reached in the majority of the questions. This manuscript reflects the consensus for TFR recommendations for LA that resulted from that meeting and multiple later reviews with the whole panel.

Results

Recommendations

Patient selection. Considering that TFR has become a new goal for selected CML patients, information about it should be shared as early as possible after the diagnosis. An extensive discussion, considering the pros and cons of TFR must be had again with the patient and family members, once the criteria to discontinue treatment have been met. Informed consent is recommended to ensure proper understanding, including information on monitoring plan, withdrawal syndrome,[20] risk of recurrence, and late relapse,[22] which make lifelong monitoring necessary.

TKI TREATMENT DURATION. Treatment duration required to consider a patient eligible for TFR has varied in different trials; a minimum of 2 years was required in most published studies. The analysis of TKI treatment duration to predict the possibilities to maintain TFR after imatinib discontinuation in the STIM study showed that patients with ≥50 months of treatment experienced significantly fewer molecular relapses than those who received imatinib for <50 months (53% vs 83%).[8,23] In EuroSKI, a prognostic analysis of 405 patients who received imatinib first-line treatment revealed that 5.8 years or more of treatment before discontinuation resulted in 63% molecular relapse-free survival at 6 months in comparison with 41% for patients who were treated for <5.8 years.[15] Although some trials have showed a trend for better chances of maintaining TFR with longer TKI treatment, none of them has demonstrated to be statistically significant.[11,14,24] In the LALNET recommendations survey, the question regarding minimal time on treatment with TKI to consider discontinuation was answered as follows: 2 years (8%), 3 years, (34%), 4 years (25%), and 5 years (33%).

When the question was asked referring only to imatinib, the minimal time on treatment before discontinuation, responses varied: 3 years (17%), 4 years (25%), and 5 years (58%).

After discussing the evidence, the consensus was to recommend a minimum of 5 years of treatment before the discontinuation for all TKIs.

LA recommendation

A minimum of 5 years of TKI treatment is recommended before considering TFR.

DMR DURATION AND qPCR ASSAY CONSIDERATIONS. Duration of deep molecular response (DMR) may be more important than duration of therapy. Most recent recommendations consider MR4.5 sustained for ≥2 years.

Several discontinuation trials established sustained MR4.0 for at least 2 years as the criteria for considering treatment discontinuation, although this specific eligibility criteria varies across TFR trials. The EURO-SKI trial found that duration of DMR (defined as MR4 or a 4-log reduction in BCR-ABL1 transcripts) before discontinuation is the most relevant factor predicting molecular relapse-free survival at 6 months. The best cutoff for DMR duration was 3.1 years, with a probability of molecular relapse-free survival of 61% for those with >3.1 years compared with 44% for those with a shorter DMR duration. Additionally, there is a linear increase in the probability of TFR maintenance per additional year in DMR in patients treated with imatinib.[15]

There was a consensus in the LA survey members that a minimum of 2 years of DMR duration is required to attempt discontinuation, keeping in mind that more evidence is being generated and more time (3 years or more) may improve outcomes. In search of the best possible outcome, the panel defined MR 4.5 international reporting scale [IS] as DMR to attempt TFR. PCR tests should be performed in standardized laboratories according to the ELN recommendations for *BCR-ABL* quantification.[6] Results should be available within 2 to 3 weeks to minimize delays in resumption of therapy when needed. For centers without access to a reliable qPCR 4.5 test that do not have the possibility to send samples to a reference center, the panel strongly suggested not attempting TFR outside of a clinical trial because an unreliable qPCR result could jeopardize patient safety.

LA recommendation

- A minimum of 2 years of sustained DMR duration (DMR, defined as MR 4.5 [BCR-ABL1 IS ≦ 0.0032%]) is required to consider discontinuation. Sustained DMR must be demonstrated on at least 4 IS qPCR tests, separated by at least 3 months, in the immediate prior 2 years.
- Confirming the DMR with a reliable qPCR (MR 4.5 IS) is recommended, no more than 30 days before treatment discontinuation.
- If adequate IS qPCR is not available, the group strongly recommends not to attempt TFR.

STATUS OF THE DISEASE AT DIAGNOSIS. All studies on TFR have excluded patients with prior history of accelerated phase or blast crisis. There was a consensus in the group to recommend that only patients in first CP be considered for TFR.

LA recommendation

Only patients in first CP CML should be considered for TFR.

TYPE OF BCR/ABL TRANSCRIPT. Atypical BCR-ABL transcripts have been described in a minority of patients with CML at diagnosis. These patients cannot be monitored with qPCR IS and thus determining major molecular response (MMR) or MR4.5 is not feasible.[25]

There was a consensus of the panel to recommend that all patients must have a typical quantifiable transcript at diagnosis that can be measured in IS.

LA recommendation

All patients considered for TFR must have a transcript at diagnosis (b3a2 [e14a2] and/or b2a2 [e13a2], typic isoform of p210).

SOKAL SCORE. In the STIM trial, Sokal score was significantly associated with the probability of molecular relapse after treatment discontinuation (80% at 72 months for high-risk Sokal vs 50% for low/intermediate-risk).[23] This has not been confirmed in subsequent trials with imatinib[15] or with second-generation TKI discontinuation.[14,24,26] NCCN 2019 and ELN 2020 guidelines, do not take into account Sokal score when considering discontinuation[18,19] but ESMO 2017 includes not having a high-risk Sokal score at diagnosis as one of the optimal criteria to support TFR attempt.[20]

The LA panel considered that if treatment discontinuation is contemplated for a patient with high-risk Sokal score, special attention must be taken to explain to the patient that there might be a higher risk of losing MMR, especially after frontline imatinib. In the LA recommendation survey, 69% of participants considered that Sokal score at diagnosis should not be considered to select patients for TFR.

LA recommendation

Sokal risk at diagnosis should not be used as a criterion to define TFR candidates, but patients with high-risk Sokal score should be informed of the possibility of a higher risk of molecular relapse.

FAILURE TO FIRST-LINE TKI. Several studies have shown that TFR after second-line TKI is possible, but to date, TFR studies have not uniformly clarified the impact of a patient's history of resistance in the probability of TFR.[10,14,15,24] The dasatinib discontinuation (DADI) study reported a significantly higher rate of molecular relapse in patients attempting TFR if they had a history of prior failure to first-line treatment: at 36 months, a TFR rate of 7.7% compared with 54% in patients without prior imatinib resistance ($P = .015$).[14] The STOP-2G-TKI study showed that the strongest adverse baseline prognostic factor for relapse was suboptimal or resistance to TKI (29.8% with previous history vs 63.6% with no previous history of resistance).[27] In contrast, the ENESTop trial analyzed TFR rates according to reason for switch in TFR patients after second-line nilotinib and did not find a similar association. Evaluable patients who

had switched to nilotinib due to intolerance, resistance, or physician preference showed similar TFR rates at 48 weeks (58.8%, 53.3%, and 61.4%, respectively).[28]

The LA group considered that most of the evidence suggests that patients with previous failure to TKI are at higher risk of relapse when attempting TFR.

The panel recommended considering the ELN definitions when evaluating whether a patient has experienced failure.

LA recommendation

TFR should only be considered in CP CML patients under treatment with second-line TKI therapy when the indication for change was due to intolerance and not for resistance.

Psychosocial considerations before and during TFR. A conversation about TFR must be planned and initiated early, ideally at diagnosis. During the TFR process, some patients may experience anxiety when faced with minor fluctuations of PCR values.[29,30] If anxiety occurs after discontinuation, the patient should be properly informed, with additional interventions if necessary (eg, psychological support).[30] Patients must be able to openly express their feelings and problems to their physicians, in a calm and nonrushed environment, participating actively in their follow-up, to guarantee a successful TFR.[31]

LA recommendation

- The psychosocial situation of each patient should be analyzed when TFR is being considered.
- Risk of molecular relapse should be clearly discussed with the patient before attempting TFR.
- During the initial information session, enough emphasis should be made on the importance of close follow-up and the need for lifelong monitoring because TFR does not mean a cure.
- During monitoring, physicians should be alert for any signs of anxiety and seek professional psychological help if needed.

Clinical and molecular monitoring during TFR. OPTIMAL FREQUENCY OF MONITORING AFTER TREATMENT DISCONTINUATION. International published studies showed different monitoring strategies during the TFR period. In the STIM trial, patients were monitored monthly during the first year with qPCR at a very high sensitivity. Between months 12 and 24, monitoring was done every 2 months and after the third year every 3 months.[8] In the EuroSKI trial, patients were monitored with a less strict schedule: from months 1 to 6 every 4 weeks, from month 7 to 12 every 6 weeks, and from the second year on, every 3 months.[15] International treatment guidelines have provided specific recommendations for monitoring BCR-ABL during the TFR period with some variability among them. The NCCN 2019 guidelines suggest monthly monitoring for the first 12 months after TKI discontinuation, every 2 months during months 13 to 24, and every 3 months thereafter.[19] ESMO guidelines suggest monthly IS qPCR during the first 6 months, every 6 weeks from months 7 to 12, and every 12 weeks thereafter.[20]

Notably, in the different studies, the vast majority of cases of molecular relapses were observed within the first 6 months of TFR. In the STIM trial, 95% of molecular relapses occurred within the first 7 months of imatinib discontinuation.[8] In the TWISTER trial, 68% of relapses occurred in the first 6 months,[13] and in the EURO-SKI trial, this was the case for 80% of the recurrences.[15]

During the TFR period, the patient's adherence to the molecular monitoring visits is vital so as to avoid a catastrophic situation in which unnoticed relapses may occur.

In the LA recommendation survey, 83% of the panel considered that BCR-ABL IS qPCR must be performed every 4 weeks during the first 6 months. Discussion on monitoring from months 6 to 12 took into account the need to make TFR an option that is safe and feasible in LATAM, also optimizing health resources. Fifty percent of the panel considered monitoring every 2 months and 33% every 3 months. As the great majority of relapses occur in the first semester, the option to control every 2 to 3 months from months 7 to 12 is recommended. Seventy percent of participants agreed that monitoring every 3 months should continue indefinitely.

If, after the 4-weekly monitoring phase, loss of response from MR4.5 to MR4.0, is detected, resuming the monthly monitoring testing for closer follow-up until the disease regains stability is recommended. As previously mentioned, it is vital that the qPCR assay used to monitor patients is standardized and expressed in the IS.

LA recommendation

- Monthly qPCR during the first 6 months after discontinuation.
- Every 2 or 3 months qPCR monitoring from months 7 to 12.
- Every 3 months qPCR from month 13, indefinitely.

DEFINITION OF MOLECULAR RELAPSE. Molecular relapse that triggered restart of TKI therapy in the STIM trial was defined as qPCR positivity with a 5-log sensitivity, confirmed in a second analysis.[8] The A-STIM trial was a multicenter observational study that first suggested that MMR can be safely used as the trigger to restart TKI therapy because ~30% of patients have fluctuation of BCR-ABL transcript levels below the MMR threshold without clinical disease recurrence. Using this criterion, TFR was estimated to be 64% at 12 months.[32] After that trial, most TFR studies have used MMR loss as the definition for relapse and the criterion for resuming therapy.[11,15,24] Accordingly, NCCN, ELN, and ESMO guidelines suggest restarting treatment when MMR is lost.[18-20]

In the LA recommendation survey, 100% of the panel agreed that loss of MMR (MMR: BCR-ABL $>$ 0.1%) should trigger resumption of TKI. TKI resumption is recommended as soon as possible, within 4 weeks from the loss of MMR.

LA recommendation

Loss of MMR, defined as BCR-ABL IS $>$0.1%, is considered molecular relapse and should trigger TKI reintroduction.

MONITORING AFTER TKI REINITIATION. In the EURO-SKI trial, in case of molecular relapse, TKI treatment was restarted and patients were

followed every 3 months until MR4.0 was achieved again, and 6 months further. After restarting treatment, in a median follow-up time of 11 months, 321 of 373 patients (86%) achieved MMR, and 302 (81%) a DMR. The median time to achieve MMR after resuming therapy was 2.8 months (95% confidence interval, 2.7-2.9) and to reach DMR 3.7 months.[15] In the observational study of CML Italian patients who discontinued TKI in clinical practice, 39% of patients resumed treatment. The frequency of monitoring after TKI restart was not reported, but 94% of the patients who were retreated regained at least MMR and 82% of them achieved DMR.[33] In a Brazilian discontinuation trial (EDI-PIO), after TKI restart, patients were monitored monthly until achieving MR4.0, then every 3 months. The median time to achieve MMR after imatinib resumption was 2.7 months.[16] In the STOP 2G-TKI trial, MMR was achieved by all patients after a median time of 2 months after dasatinib or nilotinib restart.[24] The NCCN guidelines for CML recommend TKI resumption within 4 weeks from loss of MMR, and molecular monitoring every 4 weeks until MMR is regained, then every 3 months for patients who reach MMR. Patients who fail to respond after 3 months of TKI resumption should have BCR-ABL mutation screening and monthly follow-up.[19] The French guidelines recommend, after TKI resumption, monitoring *BCR-ABL* transcripts every 3 months until an MMR and a DMR are regained and then every 3 to 6 months. If MMR is not achieved again within 6 months, they recommend screening for BCR-ABL mutations and switching therapy according to the mutation.[22] Mutations in this setting are rare, but there is a report of a patient from the ENESTfreedom trial who relapsed after treatment discontinuation and had a detectable F359V BCR-ABL1 kinase domain mutation. This patient achieved MMR after nilotinib recommencement but lost the response and had to be removed from the trial for lack of efficacy.[11] Only 1 patient from the A-STIM trial has progressed to a sudden blast crisis after imatinib resumption, after achieving MMR.[34]

In the LA recommendation survey, part of the panel considered that qPCR must be performed every 4 weeks until MMR is regained, whereas others considered it should be performed every 3 months.

LA recommendation

Patients should be monitored every 2 to 3 months after TKI reintroduction, until achieving MR4.0, then, every 3 to 6 months. If the patient does not regain MMR in 3 to 6 months, mutation screening is recommended.

Monitoring and management of withdrawal syndrome. TKI withdrawal syndrome is a well-described event that has been reported in different TFR clinical trials occurring in ~30% of patients.[35-38] It consists of musculoskeletal pain mainly in the upper body joints, shoulders, or hips, may resemble rheumatic polymyalgia, and requires multiple symptomatic treatments in 30% of patients, including nonsteroidal anti-inflammatory drugs, corticosteroids, physical therapy, or, occasionally, resumption of TKI to treat the symptoms associated with withdrawal syndrome.[38] Although 80% of events are considered mild, and usually resolve after a median of 7 months (3-30 months), 5% of patients can present with a more severe form.

Univariate and multivariate analyses identified 2 risk factors: duration of TKI treatment (risk ratio = 1.68 [1.02-2.74]) with a 93-month cutoff time, and history of prior osteoarticular symptoms (risk ratio = 1.84 [1.04-3.28]). Withdrawal syndrome seems to be a TKI class effect and its pathophysiology remains unclear.[32,39]

Patients and physicians should be aware of the possibility of TKI withdrawal syndrome before discontinuation as this can be a quality-of-life–affecting event. Although symptoms also rapidly resolved in patients who restarted TKI, this approach is not routinely recommended because, in the vast majority of patients, symptoms resolve eventually and can be controlled with appropriate treatment.[15,40] Monitoring patients to identify symptoms suggestive of withdrawal syndrome is necessary, especially those who have received TKI for >93 months or who report a history of previous osteoarticular pain.[10]

LA recommendation

- Adequate information about withdrawal syndrome should be provided to patients when considering TFR. Patients should be actively monitored for osteoarticular symptoms.

Important considerations for TFR in LA: pharmacoeconomics. The long-term treatment of CML has a huge financial impact, for patients and for the public health systems. TKI discontinuation has been associated with substantial cost savings in CML treatment. In the EURO-SKI trial, there were estimated savings of €22 million.[15] A recent Brazilian pharmacoeconomic study estimated the saving costs of $1 540 340.00 US dollars over 29 years, based on successful discontinuation of TKI in 19 patients.[41] For this reason, pharmacoeconomic analysis of CML treatment may have an important impact for LA. TFR in South America is also impaired by the lack of standardized laboratories and reimbursement for qPCR tests. Combined policies, designed by expert physicians, members of health care organizations and the pharmaceutical industry, and public health systems could bring universal solutions and provide a protocol based on evidence that is equally efficient and sustainable.

LA recommendation

- Each country should have epidemiological data about incidence, prevalence, and cost-efficiency during CML treatment.
- Pharmacoeconomic studies should be conducted as these will demonstrate the positive financial impact of TFR. This in turn will contribute to the approval of PCR testing during treatment and for TFR monitoring, making TFR feasible and safe.

Additional laboratory follow-up after discontinuation. The LA panel recommended monitoring glucose levels, glycosylated hemoglobin, and lipid profile after TKI discontinuation. Patients with CML with type 2 diabetes mellitus have reduction in fasting plasma glucose and glycosylated hemoglobin at 1 and 6 months while using imatinib.[42] In the Brazilian discontinuation trials, polycythemia, hyperglycemia, and hypertriglyceridemia were observed after stopping imatinib.[43] The French guidelines recommend monitoring of fasting glucose and glycosylated hemoglobin in diabetic patients 3 to 6 months after the discontinuation of nilotinib because of the effect of this drug on glucose metabolism.[44] Because of the drug-drug interaction of TKIs

Table 1: Comparative TFR recommendations

	LALNET	LeukemiaNET	NCCN	ESMO
Diagnostic phase	**Chronic MANDATORY**	**Chronic MANDATORY**	Chronic	Chronic
Type of transcripts	**B3a2(e14a2), or b2a2 (e13a2), typic isoform of 210 MANDATORY**	Typical e13a2 or e14a2 BCR-ABL transcripts **MINIMAL**	Quantifiable BCR-ABL transcript	Typical b2a2-or b3a2-BCR-ABL transcripts or atypical transcripts that can be quantified over a 4.5 log dynamic range
Sokal Risk	**High Sokal Risk patients** should be i nformed of the possibility of a higher risk of molecular relapse. Special attention required.	Not mentioned	Not mentioned	Non-high
Failure	Only second line due to intolerance **MANDATORY**	No failure to 1st line **MINIMAL**	Not mentioned	No failure to 1st line
TKI treatment	>5 years for all TKI **MANDATORY**	> 4 years 2nd GTKI > 5years 1st GTKI **MINIMAL**	≥3 years	>5 years
Depth of MR required	MR 4.5 **MANDATORY**	MR 4.0 (>3 years) **MINIMAL** MR 4.5 (>2 years)	MR 4.0	MR 4.5
Duration of DMR	>2 years **MANDATORY**	>2 years if MR 4.0 **MINIMAL** >3 years if MR4.0 **OPTIMAL** >2years if MR4.5 **OPTIMAL**	>2 years MR 4.0	>2 years MR 4.0-MR 4.5
Monitoring during TFR phase	Month 1-6 monthly **Month 6-12 every 2-3 m** Every 3m thereafter	Month 1-6 monthly Month 6-12 every 2 m Every 3m thereafter	Month 1-6 monthly Month 6-12 every 2m Every 3m thereafter	Month 1-6 monthly Month 6-12 every 6 weeks Every 3m thereafter
TKI reinitiation	Loss of MMR	Loss of MMR	Loss of MMR.	
Other aspects	Results within 2-3 weeks Psychosocial considerations Pharmaco-economic aspects Withdrawal syndrome management	Rapid turnaround results MANDATORY Motivated patient with structured comunication MANDATORY Patients agreement to more frequent monitoring after stopping TKI. MANDATORY	Results within 2 weeks No history AP-BC	Rapid turnaround results within 4 weeks INSTITUTIONAL

MINIMAL: minimal requirement, MANDATORY: mandatory requirement

with most statins, they also suggest monitoring cholesterol levels every 3 to 6 months after TKI discontinuation.

Thyroid dysfunction is a common adverse event with TKI therapy, in particular with second-generation TKI. Under treatment with imatinib, nilotinib, and dasatinib, thyroid abnormalities were detected in 25%, 55%, and 70%, respectively.[45] Checking T4 and thyroid-stimulating hormone levels 6 to 12 weeks after TKI discontinuation and adjusting the dose of thyroid replacement drugs, if necessary, is recommended.

More frequent monitoring of international normalized ratio values in patients taking warfarin should be done after TKI discontinuation because imatinib, dasatinib, and nilotinib usually increase oral anticoagulant levels.[46]

LA recommendation

After TKI discontinuation, additional monitoring of glucose levels, lipid profile, and other comorbidities should be done.

Discussion

Multiple studies have demonstrated that TKI cessation is feasible and safe in CML patients who have achieved a durable DMR on therapy. The concept of lifelong treatment is no longer a universal need for all patients.

To make TFR a safe and possible new goal of therapy in LA, the focus of these recommendations takes into account peculiarities of CML management in the region that justify differences with previously published recommendations (Table 1).

However, we recognize that some questions remain unanswered, some points may be debatable, and revisions to the recommendations may be needed in the future as new knowledge emerges.

There is a need for local real-world evidence on this topic but, although such data are being generated, agreement was reached on the importance and need to continue working cooperatively with colleagues and health care providers. We need to continue communicating the importance of adequate CML treatment in order to achieve each specific milestone: doing so will allow at least some patients with CML to only have to take the costly TKI treatment for a limited period of time and eventually attempt TFR. Clinical trials are still needed to solve pending issues such as biological investigations aimed at developing approaches that may expand the access to TKI discontinuation to more patients and better control leukemia stem cell (LSCs) to decrease the risk of relapse, with the ultimate idea of curing the disease in all patients.

In conclusion, the present recommendations help provide reassurance regarding the feasibility and safety of TKI treatment discontinuation in real-life clinical practice in LA, under close molecular monitoring. Resolution of TKI-related toxicity might translate into a potential health improvement for the patients, and shortening the time on therapy for at least some patients will represent significant cost savings for health systems throughout the region.

Authorship

Contribution: C.P., A.I.V., and J.C. designed the project, formulated the questions to LALNET members, ordered the answers, filled in the questionnaire, participated personally in every meeting, wrote and revised the manuscript, and approved the final version of the manuscript; V.A.P., K.P., and I.G. ordered the answers to the questions, participated personally in every meeting, wrote and revised the manuscript, and approved the final version of the manuscript; C.A., C.B., R.C., N.D., V.F., I.L., L.M., B.M., J.R.N., L.P., A.I.P., and S.U. filled in the questionnaire, wrote and revised the manuscript, approved the final version of the manuscript; and M.B. and M.C. filled in the questionnaire, revised the manuscript, and approved the final version of the manuscript.

Conflict-of-interest disclosure: C.P. received research funding (to the institution) from Pint Pharma; received speaker honoraria from Novartis, Pfizer, Bristol-Myers Squibb (BMS), Janssen, and Pint Pharma/Takeda; and served on advisory boards for Novartis and Pfizer. V.A.P. received research funding from Takeda, Dr Reddy's, Amgen, and AbbVie; and received speaker honoraria from Novartis, Janssen, Amgen, Aztra, and AbbVie. K.P. served on advisory boards for Astellas and Novartis, and received speaker honoraria from Pint Pharma, EMS, and Astellas. A.I.V. received speaker honoraria from Novartis. C.A. served on advisory boards for Novo Nordisk, Amgen, Takeda, and Legrand; and received speaker honoraria from Novo Nordisk, Janssen, Novartis, and AbbVie. C.B. served on an advisory board for Novartis, and received speaker honoraria from Novartis, BMS, and Pint Pharma. R.C. received speaker honoraria from Novartis, Janssen, and AbbVie. L.M. served on an advisory board for AstraZeneca and Novartis, and received speaker honoraria from Novartis, Amgen, Sandoz, Roche, BMS, AstraZeneca, Pint Pharma, and Janssen. B.M. received speaker honoraria from Novartis Pfizer, Pint Pharma/Takeda, BMS, and Varifarma. J.R.N. provided research services to Apellis and Pfizer; received speaker honoraria from AbbVie and Novartis; and served on advisory boards for Tecnofarma, Novartis, and AbbVie. L.P. served on an advisory board for Novartis. S.U. served on advisory boards for Novartis, Pfizer, Janssen, Roche, AbbVie, Pint Pharma, and TecnoFarma. J.C. received research support (to the institution) from BMS, Novartis, Pfizer, Sun Pharma, and Takeda, and was a consultant to Novartis, Pfizer, and Takeda. The remaining authors declare no competing financial interests.

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