Treatment-free remission in CML: who, how, and why?

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Chronic myeloid leukemia (CML) is the best example of successful targeted therapy. Today, the overall survival of patients with CML treated by using tyrosine kinase inhibitors (TKIs) is very close to that of the healthy population. The current question is: how can we further ameliorate the clinical outcome of patients with CML? Clinical trials have shown that some patients with CML in the chronic phase who achieve sustained deep molecular responses on TKI therapy can safely suspend therapy with no evidence of relapse. The long follow-up studies and the number of eligible patients have now validated the concept of treatment-free remission (ie, the ability to maintain a molecular response after stopping therapy). It should be considered as the future criterion to evaluate the success of clinical trials, especially if we want to take into account the quality of life of patients in addition to the economic aspect. Because post-TKI discontinuation follow-ups have been increasing over time with no evidence of relapse in some patients, the next step for the coming decade will be to address the topic of CML cure.

Learning Objectives

- To better understand how we can propose stopping TKI treatment in good responder patients
- To manage patients who stopped TKI treatment
- To understand that CML is one of the best models of personalized medicine

History of CML as a reference model

For years, chronic myeloid leukemia (CML) has been considered as a model disease in oncology, but the uniqueness of this model is now up for debate.[1] It all started in 1960 when, for the first time ever in malignant disease, an abnormal chromosome, called the Philadelphia chromosome (Ph), was observed in bone marrow cells from patients with CML.[2] This important discovery was the beginning of one of the most fantastic stories regarding progress in cancer research. After that premium observation in the city of Philadelphia, the following decades flourished with important discoveries toward understanding CML oncogenesis. From the description of the reciprocal chromosomal translocation t(9;22) by Janet Rowley in 1973, to the discovery of the Ph molecular counterpart (ie, the *BCR-ABL1* gene rearrangement) in 1980, which led to the creation of the mouse model by Georges Daley in 1990 (proving the importance of the *BCR-ABL1* gene in the development of the leukemia), there has been a lot of "water under the bridge."[3,4]

CML is also characterized by the clonal expansion of terminally differentiated myeloid cells originating from a leukemic stem cell. This leukemia has been chosen as a preferred model to study hematopoietic stem cells by several groups to understand the stochastic model or to determine models of hematopoiesis.[5] The disease presents itself as a chronic myeloid disorder, most commonly progressing from a chronic phase (CP-CML), through an accelerated phase, to a myeloid/lymphoid blast crisis. The notion that cancer initiation and progression involve stem-like cells together with a multistep acquisition of molecular oncogenic events over time is also important to consider.[6] However, the main reason for considering CML as a unique model relates to the phenomenon of oncogenic addiction; that is, the BCR-ABL protein, through its kinase activity, is the Achilles' heels of the leukemic cells.[7] To the best of our knowledge, there are no other cancer types in which this phenomenon is exhibited at this level. In CP-CML, leukemic hematopoiesis is dependent on the BCR-ABL tyrosine kinase with the exception of the very primitive leukemic stem cells.[8]

BCR-ABL is also a very useful cancer marker, specific to the leukemic cells, and largely used to determine residual disease after treatment from the peripheral blood.[9] Finally, this causative and functional lesion of CML led to the development of the first tyrosine kinase inhibitor (TKI) in medicine. Imatinib was the pioneer drug; today, a large family of cancer pills target adverse kinase activites.[10] Fifteen years later, studies from different centers and countries have shown that imatinib and second-generation TKIs dramatically improve the prognosis of the disease.[11,12] The efficacy of TKIs must be balanced by the adverse events induced, and CML is in particular a model to apply the primum non nocere of medicine to manage CML (ie, "first, do no harm").

Lessons from the past: how can we propose stopping treatment?

For a long time, allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been considered the sole treatment able to cure CML.[13] This belief was based on evidence that allo-HSCT can offer long-term freedom from cytogenetic or hematologic recurrence of the

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disease without the need for maintenance therapy. CML was the best indication for allo-HSCT, due to the fact that graft-versus-leukemia effect mediated by donor-derived T lymphocytes was more prominent than in other malignant conditions treated by allografting. Rather surprisingly, long-term positive quantitative reverse transcription polymerase chain reaction (qRT-PCR) results for BCR-ABL after transplantation have been reported, a finding that does not automatically imply relapse as no other signs of disease recurrence were observed.[14,15] Furthermore, most of the patients were apparently cured even though complete eradication of all leukemic cells was not achieved.[16] For the patients who were ineligible for allo-HSCT, the best treatment against CML was limited to an interferon alfa (IFN-α)–based regimen and palliative chemotherapy such as hydroxyurea.[17]

Before IFN-α was supplanted by imatinib as first-line treatment, our team, in pioneer work, showed that IFN-α could be stopped after a complete cytogenetic response (CCyR). We also showed that the rate of persistent CCyR depended on the time elapsed between CCyR and treatment discontinuation.[18] In very rare instances, some patients achieved a so-called complete molecular remission (CMR) defined, at that time, by the absence of qRT-PCR–detectable BCR-ABL transcripts. At the time of our study, the sensitivity of the detection of minimum residual disease was not so well defined. However, at our center, we proposed discontinuation of IFN-α in 21 patients with a sustained CMR (>2 years), and the follow-up on this cohort of rare patients was reported and updated a few years ago. The median follow-up after discontinuation of IFN-α was 8 years (range, 5-18 years). Nine of the 21 patients had persistent leukemic cells, with BCR-ABL transcript levels close to a major molecular response (MMR) after discontinuing IFN-α, without definite CML relapse.[19] Moreover, among the 12 patients with sustained CMR confirmed by qRT-PCR (4.5-log reduction), 1 relapsed and progressed suddenly after 12.6 years of IFN-α discontinuation and was treated with allo-HSCT. It therefore seems that low-level persistence of leukemic cells in patients after discontinuation of IFN-α treatment does not automatically lead to CML relapse. However, rare late relapses may occur even in patients with undetectable residual disease. This pattern of residual disease could be investigated by using molecular assays after allo-HSCT and IFN-α treatment. A similar pattern has emerged from the long-term follow-up of TKI-treated patients who stop treatment after achieving a good and sustained molecular remission. Taken together, these observations challenge the idea that cures require eradication of leukemic cells. This distinction also nicely illustrates the concept of "functional cure" and led John Goldman to propose, some years ago, the definition of "operational cure."[20]

Why stop TKI treatment in CML patients?

The life expectancy of patients with CML has recently been reported to be close to that in the non-CML population. The best demonstration was provided from the Karolinska Institute in Stockholm, where a total of 2662 patients with CML diagnosed between 1973 and 2013 were included in the Swedish Cancer Registry. Long-term survival estimates show that life expectancy is increasing to the levels close to those observed in the general population, with the largest improvements observed in the youngest patients.[21]

Consequently, the quality of life of patients with CML and pharmacologic/economic factors constitute the 2 main issues in the future.[22] In light of these 2 issues, the question of treatment cessation became of the utmost importance.[23] All TKIs possess off-target effects, and it would help to understand TKI's side effects and discover previous unknown toxicities. Adverse drug reactions (eg, pulmonary arterial hypertension, pleural effusion, vascular events) were unexpected and reported after approval of the TKIs. For imatinib, the first TKI used in CML, a link has been established between treatment and side effects that impair quality of life, especially in younger patients.[24,25] Until recently, the recommendation was to continue TKI treatment permanently outside clinical trials. However, mature data concerning TKI cessation have recently flourished, leading to different guidelines or recommendations. Use of TKIs is prohibited in pregnant women, which is an issue that frequently arises when treating younger women. Although CML is rare in the pediatric population, its treatment in children may also alter patient growth. In our daily practice, patients' requests are also important, and the question of whether imatinib is a lifelong treatment is frequently asked. Today, cessation of treatment is neither a dream nor a request for the Holy Grail but a reality that physicians will have to integrate into their daily practice. For CML, the concept of model comes back as a leitmotif.

Cessation of TKI for which category of patients

The proof of concept for stopping imatinib in patients with a very good response was initially brought up in a pilot study of 12 patients, which was published 10 years ago. This pilot study concerning imatinib discontinuation with stringent entry criteria produced promising results, with 6 of 12 patients remaining in molecular remission after a median 18 months of follow-up.[26] It inspired the STIM1 (Stop Imatinib) trial, which enrolled 100 patients in a multicenter study. In both studies, the criterion for stopping imatinib was solely undetectable molecular residual disease (UMRD); that is, maintained undetectable BCR-ABL1 in 5 assessments, for 2 years. At that time, the standardization of molecular biology of BCR-ABL1 quantification was not completely established, but the sensitivity of the technique at least for the sixth point was a 4.7- log reduction in BCR-ABL1 transcripts. The relapse triggering retreatment was defined by confirmed BCR-ABL1 positivity (≥1-log increase) or any loss of major molecular response (MMR) (Table 1). The results of this historical study have recently been updated (Table 2). Most recurrences (58 of 61) occurred during the first 7 months after suspension of imatinib, and 3 late relapses occurred at 19, 20, and 22 months.[27,28]

The TWISTER study, from the Australasian Leukaemia Lymphoma Group, used a similar study design. This Australasian CML8 trial enrolled patients who had received 3 years of imatinib therapy and had UMRD for 2 years (UMRD was confirmed before enrollment in a central laboratory with 4.5- log assay sensitivity).[29] With a median follow-up of 42 months, molecular recurrence was reported in 22 of 40 patients; the estimated TFR rate at 24 months was 47.1%.[12] Several studies have confirmed the feasibility of stopping treatment in patients with CML taking imatinib with deep molecular response (DMR), but the criteria repeatedly became less strict compared with the previous studies.[30-32] The A-STIM study provided evidence that stable UMRD before suspension of therapy was not essential for maintaining TFR, and some patients with low levels of detectable BCR-ABL1 after suspension of therapy can maintain TFR without losing MMR.[30] In A-STIM, molecular recurrence was defined as loss of MMR (Table 2). Most MMR losses occurred during the first 6 months, with 4 occurring in months 7 to 17.[30] In A-STIM, at 12 months after suspension of imatinib, estimated rates of recurrence-free survival (ie, no loss of MMR) were similar for patients who had occasional BCR-ABL1 positivity before enrollment (recurrence-free survival, 64%) and for those with stable UMRD before enrollment (recurrence-free survival,

Table 1. Molecular biology criteria in TFR studies

Study	Evaluation to determine eligibility for attempting TFR	Molecular monitoring during TFR	Molecular relapse definition
STIM1[27,28]	Undetectable for ≥2 y (≥50 000 *ABL* copies; >4.5-log sensitivity)	Monthly for the first year, every 2 mo in year 2, and every 3 mo thereafter	Confirmed *BCR-ABL1* positivity (≥1-log increase) or any loss of MMR
TWISTER[29]	Undetectable for ≥2 y (≥4.5-log sensitivity)	Monthly for the first year, every 2 mo in year 2, and every 3 mo thereafter	Confirmed *BCR-ABL1* positivity or any loss of MMR
A-STIM[30]	Undetectable for ≥2 y but occasional detectable BCR-ABL1 IS <0.1% (≥40 000 *ABL* copies; >4.5-log sensitivity)	Monthly for the first 12 mo, every 2 mo in year 2, and every 3 mo thereafter	Loss of MMR (BCR-ABL1 IS ≥0.1%)
KIDS[31]	Undetectable for ≥2 y, with duplicate analyses at >6 time points and a screening assessment performed in a central laboratory with ≥4.5-log sensitivity with nested RT-PCR and duplicate RQ-PCR assessments	Monthly for the first 6 mo, every 2 mo through month 12, and every 3 mo thereafter	Loss of MMR 2 consecutive assessments
ISAV[45]	Undetectable for ≥2 y (≥10 000 *ABL* copies; >4- log sensitivity) with ≥3 **RQ-PCR** tests performed locally	Monthly for the first 6 mo, then every 2 mo for 36 mo	Loss of MMR 2 consecutive assessments
EURO-SKI[33]	MR^4 in 3 consecutive assessments over the course of > 12 mo, with final confirmation of MR^4 performed in a standardized laboratory	Every 4 to 6 wk for the first year and every 3 mo in year 2 and 3	Loss of MMR
STOP 2G-TKI[34]	undetectable $MR^{4.5}$ for ≥24 mo	Monthly for the first 12 mo, every 2-3 mo in year 2, and every 3-6 mo thereafter	Loss of MMR
DADI[35]	Deep molecular response sustained for ≥1 y, with assessments every 3 mo at a central standardized laboratory (assay sensitivity, 10 copies in 200 ng total RNA; corresponding to *BCR- ABL1* IS 0.0069% or MR^4[*BCR- ABL1* IS ≤0.01% or undetectable disease in cDNA with>10 000 *ABL1* transcripts])	Monthly for the first 12 mo, every 3 mo in year 2, and every 6 mo in year 3	Loss of MR^4
ENESTFreedom[36]	$MR^{4.5}$ ≥1 y, nilotinib ≥2 y	Monthly for the first year, every 1.5 mo in year 2, and every 3 mo thereafter	Loss of MMR
ENESTop[37]	$MR^{4.5}$ ≥1 y, imatinib + nilotinib ≥3 y	Monthly for the first year, every 1.5 mo in year 2, and every 3 mo thereafter	Loss of MR4

A-STIM, According to Stop Imatinib; CMR, complete molecular response; cDNA, complementary DNA; DADI, Dasatinib Discontinuation; ENESTFreedom, Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Ph+ CML Patients; ENESTop, Treatment-free Remission After Achieving Sustained MR4.5 on Nilotinib; EURO-SKI, European Stop Tyrosine Kinase Inhibitor; ISAV, Imatinib Suspension and Validation; IS, International Scale; KIDS, Korean Imatinib Discontinuation Study; MMR, major molecular response (*BCR-ABL1* IS ≤0.1%); MR^4 *BCR-ABL1* IS ≤0.01%; $MR^{4.5}$ *BCR-ABL1* IS ≤0.0032%; RQ-PCR, real-time quantitative polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction; STOP 2G-TKI, Stop Second-Generation Tyrosine Kinase Inhibitor; TFR, treatment-free remission; TWISTER, Two Weeks of Low Molecular Weight Heparin for Distal Vein Thrombosis.

Table 2. Published Clinical studies of TKI discontinuation in patients with CP-CML

Study trials of imatinib discontinuation	N	Treatment before discontinuation	TFR	Median follow-up time, mo
STIM1[27,28]	100	IFN then imatinib for ≥3 y	43% at 6 mo 38% at 60 mo	77
KIDS[31]	156		59% at 24 mo	27
TWISTER[29]	40	Imatinib for ≥3 y	47% at 24 mo	42
ASTIM[30]	80	Imatinib for ≥3 y	64% at 24 mo	23
ISAV[45]	112	IFN	48% at 36 mo	22
EURO-SKI[33,*]	755	TKI ≥3 y		Preliminary results 61% at 6 mo
STOP 2G-TKI pilot[34]	60	Nilotinib or dasatinib	63% at 12 mo 54% at 48 mo	47
ENESTFreedom[36]	175	Nilotinib front line	52% at 11 mo	11
ENESTop[37,*]	117	Second-line nilotinib (≥3 y total; ≥2 y nilotinib)	58% at 11 mo	11
DADI[35]	156	Dasatinib	49% at 6 mo 48% at 12 mo	20

*EURO-SKI and ENESTop are currently submitted.

65%). Similar findings were also observed in studies such as KIDS (Korean Imatinib Discontinuation Study).[31] Among 90 patients enrolled in KIDS with a minimum follow-up of 12 months (median follow-up, 26.6 months), the probability of sustained MMR at 12 months was 62.2%. Several other studies have been reported with similar results.[32]

Recently, a meta-analysis was reported from 15 different cohort studies, involving 509 patients who stopped imatinib in molecular response (MR), including the STIM and A-STIM studies.[32] The overall rate of molecular relapse was 51%; after 6 months of follow-up, it was 41%, confirming that 80% of molecular relapses occurred in the first 6 months.

The number of patients who are stopping TKI treatment is increasing over time

A trial evaluating molecular recurrence to trigger re-treatment in a larger population of patients than those from the previous studies has been proposed by the European Leukemia Net. Wider criteria were proposed in the EURO-SKI study for performing a robust statistical analysis. Patients must have received TKI therapy for 3 years (including frontline therapy, second-line therapy due to toxicity of frontline therapy, and/or TKI combination therapy) and must have maintained molecular recurrence (MR)^4 for 1 year; MR was defined as loss of MMR.[33] A total of 821 patients with CP-CML from 11 different European countries were included. A total of 755 patients had assessable molecular data for the estimation of molecular recurrence- and treatment-free survival. Of these patients, 388 had an event, 373 lost MMR, 11 had a TKI restart in MMR, and 4 died in MMR. The molecular recurrence- and treatment-free survival at 6 months was 60% (95% confidence interval [CI], 56-63) and 49% (95% CI, 45-52) at 24 months. Eighty percent of patients regained MR^4 after treatment restart at the last update. At the time of evaluation, most patients regained MR^4 and, importantly, no progression to advanced disease phase was noted.

A prognostic modeling sample was performed in patients treated with imatinib (N = 448).[33] Univariate analysis showed no significant association between age, sex, depth of MR (MR$^{4.5}$ vs no MR$^{4.5}$), or any variable part of the Sokal, EURO, EUTOS, or EUTOS long-term survival scores. Treatment duration with imatinib and MR$^{4.5}$ duration significantly ($P < .001$) correlated with MMR status at 6 months. A cutoff at ~6 years was identified, with the minimal P value approach suggesting that patients should be treated for at least 6 years; these data need to be confirmed. Taking into account the number of months without treatment and the cost of imatinib in each of the 11 European countries, the total estimated savings are 22 million euros at the last analysis.[33] These savings will continue to increase in EURO-SKI and other studies, even despite the spread in Europe and the United States of generic imatinib. They will potentially help compensate or balance the expense of additional molecular biology investigations and visits to the physician due to TKI withdrawal syndrome. These data have been applied only for imatinib, which is now a generic, but can be applied to the second generation of TKIs.

Another interesting study from the United Kingdom (DESTINY [De-Escalation and Stopping Therapy with Imatinib, Nilotinib or sprYcel]) attempted to study de-escalation of the TKI dose for patients with CML and stable MMR.[34] The interim analysis reported that 174 patients decreased TKI treatment to one-half the standard dose. Recurrence (loss of MMR) was significantly lower in the MR^4 cohort compared with the MMR cohort. It means that the reduction of TKI dose after achievement of MR would also be an option for patients who are eligible for TKI cessation.

Stopping second-generation TKI

The feasibility of TFR after nilotinib or dasatinib has also been shown. A pilot academic study (STOP 2G-TKI) enrolled 60 patients who had received 3 years of TKI therapy, were currently receiving either nilotinib or dasatinib as frontline therapy or after imatinib, and had maintained MR$^{4.5}$ with UMRD for 2 years.[35] With a median follow-up of 47 months (range, 12-65 months), the estimated rate of TFR (no loss of MMR) at 12 months and 48 months was 63.3% and 53.7%, respectively. Previous suboptimal response or TKI resistance was the only baseline factor associated with significantly worse outcome. In other words, the best results were obtained for de novo patients or patients who were treated with second-generation TKIs because they were intolerant to imatinib. Comparable results with similar factors were reported from other academic studies.

The Japanese DADI study evaluated TFR after suspension of dasatinib as second-line therapy or beyond.[36] Sustained DMR for >1 year was required before the suspension of therapy. Evaluation of BCR-ABL1 levels was atypically performed at a central laboratory with standardization close to that of the IS. With a median follow-up of 20 months (interquartile range, 16.5-24 months), among 63 patients

who attempted TFR, DMR was maintained in 30 patients, and 33 patients had MR; the probability of TFR was 49% and 48% (95% CI, 35-59) at 6 and 12 months, respectively. All molecular relapses occurred within 7 months of stopping dasatinib therapy, and upon treatment re-initiation (dasatinib, n = 32; nilotinib, n = 1), all 33 patients with MR regained DMR within 6 months, and the majority (n = 29) did so within 3 months.

Pharmaceutical companies have performed studies for patients treated with nilotinib. The ENESTfreedom trial enrolled 215 patients to specifically investigate TFR after frontline nilotinib treatment (3 years) in sustained $MR^{4.5}$ for >1 year.[37] Ninety-eight of 190 evaluable patients (51.6%) remained in TFR after 12 months (48 weeks primary endpoint). Nearly all patients who reinitiated nilotinib due to loss of MMR rapidly regained MMR (98.8%) and $MR^{4.5}$ (88.4%).

ENESTop is a phase 2 study of patients with CP-CML treated for at least 3 years, initially with imatinib and then switched to nilotinib for at least 2 years.[38] Some patients continued to take nilotinib for another year to consolidate their response. After stopping nilotinib, 58% of patients remained in TFR at 12 months (48 weeks). The remaining 42% lost their MMR and needed to restart nilotinib. Almost everyone (98%) who restarted therapy soon regained their MMR (a 3-log reduction or better), including 92% who regained $MR^{4.5}$. The median time to regain $MR^{4.5}$ was 13 weeks.

The advantage of second-generation TKIs is that they induce a deeper response and can be proposed to more patients with CML with criteria for stopping therapy such as sustained DMR in shorter amounts of time than for imatinib. It increases the number of candidates for TFR. In light of the results obtained from the stopping trials with second-generation TKIs, there is no proof that the results of TFR will be higher compared with imatinib. Thus, the rate of molecular recurrence seems to be reproducible whatever the TKI, as though an intrinsic factor, inherent to the disease, is responsible for these results and the rate of molecular recurrence after stopping TKI. The recent results regarding the superiority of bosutinib compared with imatinib for CP-CML de novo could offer another possibility for inducing DMR, particularly for patients who are ineligible for nilotinib and dasatinib therapy.[39]

TKI withdrawal syndrome: a new entity

Some patients reported musculoskeletal and joint pain after stopping imatinib therapy. This outcome was more specifically investigated in a subcohort of the EURO-SKI trial, in which it occurred in 15 of 50 of patients.[40] The pain was localized to various parts of the body, including the shoulder and hip regions and/or extremities, sometimes resembling polymyalgia rheumatica. Symptoms were mild in most individuals, leading only to the use of nonprescription drugs (paracetamol or a nonsteroidal anti-inflammatory drug), but some patients reported more severe manifestations that interfered with everyday activities and required steroid therapy. Over time, these symptoms seemed to resolve. The rate of molecular relapse in patients with musculoskeletal pain did not differ from those without these symptoms. In addition, in the STIM2 trial, 21% of the patients reported musculoskeletal symptoms compatible with the "TKI withdrawal syndrome."[41] This phenomenon is not restricted to imatinib pretreatment. This syndrome also affected patients who stopped nilotinib. For instance, in the ENESTfreedom trial, musculoskeletal pain–related events were reported in 24.7% of patients in the TFR phase compared with 16.3% in the consolidation phase.[36] We still do not know the underlying mechanisms, but the long-term inhibition of C-Kit by TKI could explain this peculiar syndrome. Accordingly, nilotinib, in a proof-of-concept study, has been reported to treat spondyloarthritis.[42] The mast cells could be the candidate target cells responsible for this disease and TKI withdrawal syndrome. Investigations are in progress to explore the potential link with such syndromes.[43]

How many times can we stop TKI?

The future of patients who experience molecular recurrence after discontinuing TKI remains a major issue. The results of a French multicenter study (RE-STIM) have been reported.[44] TFR in patients with DMR who attempted a second discontinuation of TKI therapy was evaluated. Based on the loss of MMR criterion as a trigger for treatment resumption, a TFR rate of 42% at 24 months was found. Delayed relapses over time led to a TFR rate of 34% at 36 months. The only factor associated with improved TFR was the persistence of undetectable molecular disease at 6 months from the first discontinuation. The TFR probability at 24 months increased to 72% (95% CI, 48.8-100.0) in patients remaining in undetectable $MR^{4.5}$ at 6 months after the first discontinuation versus 36% (95% CI, 15.1-44.6) in others. Thus, close molecular monitoring of patients attempting a second TKI discontinuation is necessary even after 24 months. A second TKI discontinuation attempt would preferably be reserved for patients with CP-CML relapsing >6 months after the first TKI cessation. These data should be confirmed in a larger study but must be taken into account when writing recommendations.

Clinical and biological factors associated with successful TFR

A substantial proportion of participants in TFR trials experience molecular relapse.[43-45] Although the majority of these patients can regain DMRs upon re-initiation of therapy, a more complete understanding of which patients are most likely to achieve TFR would lead to stronger eligibility criteria and may help ease patient concerns about attempting TFR.[23,27,43,45]

Studies have suggested that several patient characteristics seem to be associated with successful TFR, but the results have not been consistent among studies. A multivariate analysis of data from STIM1 identified low Sokal risk score as an independent predictor of successful TFR.[28] In TWISTER, no effect of Sokal risk score was detected, but long (>12 months) duration of IFN therapy before imatinib and short (≤9 months) time to achieve UMRD after switching from IFN to imatinib were associated with higher rates of successful TFR.[20] In KIDS, factors associated with successful TFR included longer (≥62 months) imatinib duration, presence of imatinib withdrawal syndrome, and negative digital PCR at the time of imatinib cessation.[31] In the ISAV study, age (≥45 years) and negative digital PCR at enrollment were associated with successful TFR; no patients <45 years of age with positive digital PCR at enrollment had successful TFR at 24 months.[46] In A-STIM and a Japanese study using similar criteria (JALSG-STIM213), no significant predictive factors were identified.[30,47] However, as in TWISTER, there was a trend ($P = .061$) for lower rates of molecular relapse among patients with previous IFN therapy versus those without previous IFN therapy.[29,30] Among patients attempting TFR after nilotinib or dasatinib therapy in STOP 2G-TKI, a history of suboptimal response or resistance to imatinib was significantly ($P = .04$) associated with a decreased probability of successful TFR.

Table 3. Author's recommendation or personal guidance of stopping TKIS in good responder patients outside a clinical trial

Key prerequisites
Declaration to an international or national registry
Very strict molecular monitoring with a certified laboratory* expressing the results on the IS with sensitivity strictly >4-log
No patient history of resistance to treatment
Patients
Patients with CP-CML treated with TKI for at least 5 y
Three points of BCR-ABL level per year mandatory with MR^4 during 3 following years or $MR^{4.5}$ during 2 following years (1 point in MR^4 could be acceptable)
Molecular monitoring during TFR
Monthly for the first 12 mo, every 2 mo in year 2, and every 3 mo thereafter
Molecular relapse
Defined by loss of MMR or BCR-ABL level IS >0.1%, which trigger for re-initiation of TKI therapy
Re-challenge the treatment with the same TKI in the following month after loss of MMR

*In Europe, the laboratories have been certified by the European Leukemia Net (www.leukemia-net.org).

Some analyses have identified immunologic factors associated with molecular relapse–free survival. In DADI, high natural killer (NK) cell (CD3−/CD56+ [$P = .017$] and CD16+/CD56+ [$P = .0053$]) and NK cell large granular lymphocyte (CD56+/CD57+; $P = .022$) counts and low γδ+ T-cell ($P = .0022$) and CD4+ regulatory T-cell ($P = .011$) counts were associated with successful TFR.[35] In addition, patients with higher NK cell counts at the time of TKI discontinuation were more likely to have successful TFR in separate substudies from STIM1 ($P = .015$) and EURO-SKI ($P = .001$).[48,49] In both substudies, the higher NK cell count in nonrelapsing patients was due to increased frequencies of mature CD56dim cells relative to CD56bright cells. A separate substudy from EURO-SKI found that patients with lower frequencies of CD86-positive plasmacytoid dendritic cells had a higher rate of successful TFR ($P < .001$).[50] Studies are under way to better define the immunologic factors. We suggest that immunologic factors control the late molecular relapse and the plateau phase of the TFR curves.[43]

From the clinical trials to real life: patient's point of view

Are there enough data to propose guidelines in real life? The most recent recommendations of the National Comprehensive Cancer Network dare to take the step by proposing to stop TKI outside a clinical trial for adult patients in stable and sustained MR4 during the 2 following years.[51] The recommendations in the other 2 recent reviews were also different.[43,45] One review states that despite the defined safe criteria, discontinuation of therapy is still experimental and should be restricted to clinical trials or registries. The other review claims that recommendations have to be edited for patients with CML who have achieved a stable DMR with long-term TKI therapy. We are definitely entering the TFR era for the benefit of the patients because the CML advocate groups consider this topic of utmost importance (https://www.facebook.com/groups/CMLTFR/). Giora Sharf from Israel said "we have to remember that with all the excitement of being able to stop treatment which is the closest we can get to cure at this time, this is relevant only for about 25% of the patients. The main goals of treatment for CML patients are still achievement of good response to prevent progression and quality of life." Jan Geissler from Germany added that "we must remember that CML patients in DMR are considered to be in the 'safe haven' under continued TKI therapy, having a life expectancy similar to the normal population. Stopping TKI therapies might be a great opportunity for them to live a normal life without the physical and economic burden of CML treatment. However, their life should not be put at unreasonable risk by less stringent management of treatment discontinuation, which, according to surveys, is already the case in some oncology practices today. Stopping should only be done in centres that fulfil all institutional requirements to stop, including standardized, sensitive PCR, and the ability to monitor patients after discontinuation very closely. A single CML patient in DMR then lost to progression due to poor discontinuation management would be one too many."

This response illustrates that we cannot manage patients with CML without taking into account what they wish for, and in that sense, CML is also a reference model for working hand-in-hand with our patients.

Finally, I propose my personal guidance for stopping TKI in good responder patients. These criteria are stricter than the most recent trials to ensure safety and take into account the disparities in the different countries (Table 3).

Conclusions

Are there any differences in the meanings between TFR and "cure"? I say, probably yes. In the most rigorous sense, curing CML would require complete eradication of CML cells from the patient's body, including leukemic stem cells. This level of cure has remained elusive and may not be necessary because even patients in remission after HSCT can have detectable BCR-ABL1. We must keep in mind that BCR-ABL has been detectable in healthy individuals.[52,53] An operational cure, in which patients with minimal levels of residual disease remain in remission without requiring ongoing treatment, may be a more appropriate goal. Results from TFR studies to date suggest that some patients with CML with sustained deep DMR may be able to achieve an operational cure. Comparable concepts are being discussed in other diseases, such as breast cancer and HIV infection.[54,55]

Convincing results from the CML studies have validated the concept of TFR, which have become the main criteria for clinical trials. CML will continue to be a model of hematology and cancer, but now, the subject of disease curability is the next step to reach for all patients.

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