Treatment Outcomes in Chronic Myeloid Leukemia: Does One Size Fit All?

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ABSTRACT

With the success of tyrosine kinase inhibitors (TKIs) in achieving next-to-normal overall survival in chronic myeloid leukemia (CML), treatment-free remission (TFR) has become a significant goal in the management of this disease. Discontinuation of therapy is attractive to both patients and physicians because maintaining a stable BCR-ABL transcript level without therapy would imply true operational CML cure. With TFR, patients are not exposed to unknown long-term adverse effects of TKIs and common adverse effects that may affect quality of life. Several factors need to be considered before attempting TFR, because this goal is not appropriate for a significant proportion of patients with CML. Patient-related factors, CML response to therapy and its duration, monitoring capacity, patient preferences and compliance with monitoring, and economic factors influence the decision to attempt to discontinue TKIs. Unfortunately, only 50% of patients are appropriate candidates for discontinuation of treatment. Of those, another 50% maintain stable disease while off TKIs. This means that merely 25% of patients achieve TFR. Further optimization and research are required to be able to extend this treatment goal to a larger population of patients. Although TFR is attractive and desirable, this goal is not a one-size-fits-all approach, and we should continue to focus on patients with CML having a normal OS with the best quality of life possible.

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The prognosis of chronic myeloid leukemia (CML) has greatly improved since the clinical use of tyrosine kinase inhibitors (TKIs) started with imatinib in the early 2000s.¹ It is now considered a chronic disease, with its incidence being stable and prevalence increasing due to prolonged survival.^{2,3} Life expectancy has approached that of the general population, with 5-year survival only slightly lower in patients with CML.⁴ This benefit is observed in all age groups, but especially in patients as young as 55 years.⁵ The main reason for patients not reaching general population life expectancy seems to lie in the increased incidence of other malignancies and cardiovascular morbidity.^{5–9} This milestone, however, would never have been possible without widespread treatment and availability of TKIs, resulting in disease control and molecular response.

Treatment-free remission (TFR) has emerged as a new goal for many patients with CML as a distinct outcome other than overall survival (OS). This is driven by the absence of long-term safety data of TKIs beyond 10 years and the idea of reducing severe and mild TKI-related adverse effects, which may result in improved quality of life (QoL).^{10,11} Enabling this approach are the long-term outcomes in the different TKI trials showing that a substantial proportion of patients may achieve a deep molecular response (DMR)^{6,12–15} and maintain it after discontinuation of the medication.¹⁶ This shift in therapy goals is still debated and has not yet been adopted in routine clinical care outside of clinical trials. This review discusses points for and against widely adopting TFR as a clinical outcome above OS in routine practice.

TFR and Factors That Influence It

What Is TFR?

TFR has been defined as the maintenance of stable low levels of minimal residual disease (MRD) or undetectable MRD without the need for ongoing treatment.¹⁷ Some investigators consider this an operational definition of cure,¹⁷ as opposed to a functional one for those remaining on therapy as coined by John Goldman.¹⁸ MRD is measured with real-time PCR of the BCR-ABL transcript, with the resulting measurement defining degrees of molecular

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response. Major molecular response (MMR) is a BCR-ABL $\leq 0.1\%$ (3-log reduction), and DMR is a BCR-ABL $\leq 0.01\%$ (4-log reduction; MR4). As discussed, maintenance of prolonged responses correlates with favorable outcomes and near-normal OS. Patients now need to maintain an MMR or deeper response without restarting therapy to remain in TFR. This is not a novel idea, as it was observed in patients with CML previously treated with interferon who had to stop the drug but continued to experience cytogenetic remission despite detectable BCR-ABL transcripts.^{19,20} This was the initial proof of concept that TFR was possible in CML and that its principles could be extrapolated to TKI therapy.

CML and Patient-Related Factors Influencing TFR

Important questions to ask are in whom and when is it appropriate to attempt TFR? Discontinuation trials have used different inclusion criteria to consider stopping treatment. Apart from molecular responses determining disease control, several patient factors need to be considered before attempting discontinuation. Not all CML is the same, and not all patients have the same risks related to disease progression, response to TKIs, age, or comorbidities.

Disease risk in CML plays an important part in the decision to discontinue therapy. Patients at high risk of leukemia-related death (LRD), as assessed by a risk assessment score, should probably remain on TKI treatment to avoid this outcome. Risk assessment scores such as the Sokal score²¹ have been used since the pre-TKI era and continue to be valid in predicting response and survival. Most recently, other scores, such as the EUTOS long-term survival score (ELTS), try to more accurately predict the probability of LRD in patients treated with imatinib,²² because LRD is not a frequent outcome in patients with CML anymore. ELTS has better prediction capacity in LRD because the weight of age is lower in this score.²³ Even though this score classifies patients more precisely, the Sokal score has historically been used in clinical trials and in some proposed optimal criteria for discontinuation.^{3,17} Some guidelines^{3,17} recommend non-high Sokal scores to attempt TFR, but this is a flexible point, depending on other factors that are further discussed later.

Patients with CML may present with additional cytogenetic abnormalities to the standard translocation (9;22)(q34;q11). Additional cytogenetic abnormalities are considered to have worse prognosis and response to TKIs,^{24–26} which is why patients bearing these clonal abnormalities should not be considered for TFR. Special clinical trials for this group that comprises only approximately 5% to 7% of patients with CML^{24,25,27} should

be considered if TFR is to be sought as an outcome for them in the future.

Age is another driver for patients and physicians to consider an attempt at TFR. Age is important in prognosis and outcomes,²⁸ and is included and weighed into risk assessment scores. Different age groups have distinct behaviors and lifestyles, work and careers, financial situations, and goals. Patients and physicians may be more inclined to consider drug discontinuation among younger age groups who may not wish to be tied to a prescription medication throughout their lives. This especially applies to women who are considering pregnancy, as outlined later. Everyone has the right to attempt TFR in the proper medical context, with age itself not being an indication or contraindication for this. Decision-making is influenced by age but not dictated by it.

Comorbidities are an essential element of decision-making with regard to which TKI to prescribe as first-line therapy and, along with disease risk, age, and adverse effect profile, are considered when choosing a TKI upfront. Guidelines^{3,29,30} exist with recommendations for appropriate TKI prescription. Imatinib and bosutinib are fairly safe, and no strong contraindication exists to their use. Dasatinib might not be appropriate in the setting of previous lung disease, including pulmonary hypertension and fibrosis. Nilotinib should be avoided in patients with a history of cardiovascular disease and diabetes. The choice of TKI as a result of comorbidities might ultimately play a role in the possibility and chances for a patient to attempt TFR. As discussed later, second-generation TKIs (2g-TKIs) are more potent and can achieve deeper and faster molecular responses than imatinib,³⁰ providing a better opportunity for TFR.

Feasibility and Previous Treatment-Related Factors

Identifying a patient suitable for CML treatment discontinuation is a first step toward attempting TFR, with a second and equally important step being determining that CML has had an appropriate duration and depth of response to TKI treatment. These factors have been associated with better chances of achieving and maintaining TFR in discontinuation trials and are part of general recommendations.^{3,29–31} More than 50 TKI discontinuation trials have been published,³² all of them agreeing on certain depth and duration of response, but criteria vary across them.¹⁶

The depth of molecular response has shown some correlation with probability of TFR. As mentioned, different criteria have been used across studies, with some requiring $\geq$ MR4 or $\geq$ MR4.5 to be achieved before attempting TFR. However, some data show that MMR and not complete molecular response (5-log

reduction) can have significant sustained TFR,³³ with others reporting higher risk of molecular relapse.³⁴ Overall, some degree of depth of response is required, but a specific cutoff is currently unknown. Therefore, to clarify this question, TFR should only be attempted in patients with a response less than MR4 (DMR) within a clinical trial setting.

Duration of DMR might be more important than overall duration of TKI treatment, as shown in prognostic modeling from the EURO-SKI trial,³⁵ but specifically designed trials are needed to explore this aspect and allow recommendations.³² In addition, the velocity at which the BCR-ABL transcript decreases when starting treatment is prognostic of disease progression,^{36,37} possibly influencing future TFR attempts and opening the door to more widespread upfront use of potent 2g-TKIs. Halving time in the first 3 months was the strongest independent predictor of sustained TFR in a recent study.³⁸ There is no clear evidence showing that changing therapy from imatinib to a 2g-TKI will achieve

a deeper molecular response and allow an attempt at discontinuation, with this practice being controversial.³⁰

After factoring in the previously discussed conditions, patients might be eligible to attempt TFR. Table 1 summarizes criteria for appropriately selecting patients for TFR. It is important to note that only approximately 40% to 50% of patients will attain a DMR^{6,13,14} with TKIs and will therefore be eligible to discontinue treatment. This number does not account for patients not eligible based on any of the other criteria. Once TFR is attempted, data from the imatinib discontinuation trials estimate a long-term average of sustained TFR of approximately 40% to 50%.^{39,40} Similarly, dasatinib discontinuation trials reported approximately 48% to 63%^{41–43} maintenance of TFR and nilotinib trials reported 48% to 68%.^{44–46} A small trend favors 2g-TKIs in the rates of achieving sustained TFR. Detailed results of the discontinuation trials and their inclusion characteristics are outside of the scope of this review and can be found elsewhere.^{16,47,48} No evidence is available regarding discontinuation of bosutinib or ponatinib.

Table 1. Comparison of Proposed Optimal Criteria for Attempting Treatment-Free Remission

NCCN Guidelines 2019 ²⁹	ELN Guidelines 2020 ³⁰	ESMO Guidelines 2017 ³	Hughes et al ¹⁷	French CML Study Group Recommendations ³¹
Age ≥18 y	—	—	—	Age >18 y
—	—	Sokal score ²¹ non-high at diagnosis	Sokal score ²¹ non-high at diagnosis	—
Chronic-phase CML (no prior blast- or accelerated-phase CML)	Chronic-phase disease	Chronic-phase disease	Chronic phase only	Chronic phase only
TKI therapy for ≥3 y	TKI therapy >5 y ^a or >4 y for 2g-TKI	TKI therapy >5 y	TKI therapy >8 y	TKI therapy >5 y
Prior evidence of quantifiable BCR-ABL1 transcript	Typical b2a2 or b3a2 BCR-ABL1 transcript	Typical b2a2 or b3a2 BCR-ABL1 transcript or atypical quantifiable transcript	Typical b2a2 or b3a2 (e13a2 or e14a2) BCR-ABL1 transcript	e13a2, e14a2, or e13a2 + e14a2 BCR-ABL1 transcript
Stable molecular response (MR4; BCR-ABL1 ≤0.01%) for ≥2 y on ≥4 tests ≥3 mo apart	DMR >3 y if MR4 ^a DMR >2 y if MR4.5 ^a MR4 or greater >2 y	MR4.5 reached Duration of DMR (MR4 or MR4.5) >2 y	MR4.5 depth of DMR Duration of DMR >2 y	MR4.5 in ≥4 consecutive tests Duration of DMR ≥2 y
Access to reliable qPCR with sensitivity detection of at least MR4.5 with results within 2 wk	Access to high-quality qPCR with rapid turnaround test results	Institutional criteria met: 1. Availability of high-quality qPCR 2. Turnaround results within 4 wk	Institutional criteria met: 1. Availability of high-quality qPCR 2. Turnaround results within 4 wk	—
Monthly molecular testing for 1 y, every 6 wk for second year, and every 12 wk thereafter	Monthly molecular testing for 6 mo, every 2 mo for months 6–12, and every 3 mo thereafter	3. PCR capacity every 4–6 wk	3. PCR capacity every 4–6 wk	—
Resumption of TKI within 4 wk of loss of MMR	Motivated patient with structured communication	4. Structured follow-up to enable rapid intervention if BCR-ABL1 is increasing	4. Structured follow-up to enable rapid intervention if BCR-ABL1 is increasing	—
Consultation with CML specialty center to review appropriateness of TKI discontinuation	First-line therapy, or second-line if intolerance was reason for TKI change No prior treatment failure	Optimal response to first-line therapy	Optimal response to first-line therapy	No allo-SCT, suboptimal response or warning, progression, or resistance

Abbreviations: 2g-TKI, second-generation tyrosine kinase inhibitor; allo-SCT, allogeneic stem cell transplant; CML, chronic myeloid leukemia; DMR, deep molecular response; ELN, European LeukemiaNet; ESMO, European Society for Medical Oncology; MMR, major molecular response; MR4, molecular response of 4-log reduction; MR4.5, molecular response of 4.5-log reduction; qPCR, quantitative PCR; TKI, tyrosine kinase inhibitor.

^aOptimal.

QoL Aspects

QoL has improved substantially since TKIs became standard therapy for CML.⁴⁹ Even though huge strides have been made in this area, patients with CML receiving TKIs still do not have QoL equal that of the general population. This is especially significant in younger patients (age 18–39 y) and women, who have been shown to present with limitations in work and daily activities due to physical and emotional problems linked to treatment and disease.¹⁰ Common adverse effects vary among TKIs, but fatigue, muscle pains, nausea and vomiting, and edema are frequently encountered.⁵⁰

Because QoL is not equal to that of the general population, some investigators proposed that TKI discontinuation would bring benefits to patients with CML and avoid major adverse effects, such as pleural effusion and cardiovascular events. A specific study examined QoL changes in patients who discontinued imatinib, showing improvement in TKI-related symptoms but, in contrast, the appearance of new musculoskeletal pain, fatigue, and pruritus.⁵¹ Overall, some benefit was noticed in patients, but no significant improvement in physical or mental health was reported with TKI discontinuation. Treatment discontinuation has prompted the identification of TKI withdrawal syndrome,⁵² characterized mainly by musculoskeletal pain, which can last for months. It is managed with acetaminophen, nonsteroidal anti-inflammatory drugs, or steroids and can occur in approximately 20% to 40% of patients. It seems that TKI withdrawal can occur regardless of the TKI agent used.^{53,54} The appearance of TKI withdrawal syndrome may abrogate some of the benefit of discontinuing therapy with the goal of relieving symptoms and improve QoL, although it is easily treated.

Another consideration for attempting TFR in women of childbearing age is that they may wish to become pregnant. TKIs are not known to severely affect fertility, but evidence suggests that they can have effects on fetal development and predispose patients to poor obstetric outcomes.⁵⁵ Breastfeeding while receiving TKIs is not recommended, because imatinib, nilotinib, and dasatinib can be found in breast milk, with no data for bosutinib. Even though pregnancy can be carried out safely in patients with CML with appropriate planning,⁵⁵ with some cases of uneventful pregnancies while receiving TKI therapy,⁵⁶ most still advocate for TFR as a better goal for this patient population, or for a conversion of therapy to interferon.⁵⁵

Patient Preferences

Just because patients are good candidates and meet criteria to attempt TFR does not mean that they are actually willing to discontinue their TKI. Factoring in psychologic aspects, motivations, and preferences is a key aspect of this approach. Although several studies

have shown that patients are willing to stop treatment, there is a fraction who are reluctant to embrace the idea, mainly driven by the fear of consequences, including risk of recurrence.^{57–60} Interestingly, many of these patients are receiving long-term TKI therapy. In contrast, numerous patients are motivated to discontinue treatment due to TKI toxicity and convenience,⁵⁸ not to mention economic factors.⁵⁷

Physicians must take into account potential psychologic issues that can be associated with TFR. Anxiety generated by fluctuating BCR-ABL levels during follow-up needs to be considered.⁵⁴ It has been proposed that screening for potential psychologic issues associated with TFR should be part of routine monitoring in follow-up,⁵⁴ although no validated or standardized method exists. Physicians must also take into account a possible perception or idea of failure that could arise in patients who do not achieve TFR and require return to treatment. Even though patients regain control of CML molecular response by restarting TKI without progression or loss of response,^{35,39–41,45} and a second attempt at discontinuation can be tried safely,^{61,62} the psychological impact on the patient cannot be predicted.

Economic Factors

Even though economic considerations should be a secondary reason for attempting TFR, they still play a significant role from the point of view of both the patient and the healthcare system. TFR might reduce the overall cost of treating CML by discontinuing expensive drugs that carry high yearly prices. From a patient perspective of needing to cover these costs by buying medication, it is a straightforward decision. As mentioned, patients are willing to attempt TFR for economic reasons,⁵⁷ even though this ideally should not be a driver of decision-making.

One consideration with the use of 2g-TKIs as first-line treatments has been that even if upfront costs are higher than with imatinib, after discontinuation, cost-effectiveness will balance out and be favorable toward 2g-TKIs. This was investigated in a 10-year simulation concluding that imatinib was still the most cost-effective approach even after incorporating TFR.⁶³ When only considering TFR as the goal, the cost saved with imatinib was less than that with 2g-TKIs, because fewer patients can attempt TFR with imatinib. We must remember that, on average, 75% of patients continue on TKI therapy in the long term because they are not candidates for attempting TFR or will not be able to maintain TFR. This analysis does not justify starting 2g-TKI upfront for the sole purpose of achieving rapid TFR and improving cost-effectiveness of treatment. This was confirmed in an analytic model that showed that 2g-TKI price has to decrease significantly to become cost-effective compared with imatinib.⁶⁴

The approval of generic 2g-TKIs may alter this balance and turn out to be a feasible strategy. Overall, a randomized trial between a higher upfront cost 2g-TKI with TFR attempt versus lifelong therapy on a cheaper drug such as imatinib is needed to clarify this question.

Regardless of the TKIs chosen upfront, some studies have shown that discontinuing TKI therapy is eventually a cost-effective strategy.⁶⁵ Unfortunately, the more frequent BCR-ABL monitoring required with TFR surveillance and frequent physician visits have not been factored into studies, and the overall cost-effectiveness of this strategy requires further research.

Monitoring Capacity and Physician Aspects

Monitoring capacity is a key element in attempting TFR. Guidelines have clear recommendations on how to monitor the BCR-ABL transcript once drug discontinuation has occurred^{3,29,30} (Table 1). Rapid test result turnaround within 2 to 4 weeks is suggested.^{3,17,29,30} These strict guidelines pose important problems for institutions and physicians that may not have the resources available to follow them. Attempting TFR with a lack of capacity to monitor is discouraged. Physicians caring for patients with CML require more education on guidelines and monitoring if they are to attempt TFR.⁶⁶ When we extrapolate data from routine monitoring while on treatment, it has been shown that guidelines are not consistently translated into routine practice, with fewer than half of patients with CML followed appropriately.^{67,68} This is a dangerous situation when attempting TFR because patients require

close follow-up, especially in the first 6 months when most relapses occur.⁶⁹ Barriers identified for physicians adhering to guidelines include resource availability and lack of time to search guidelines.⁶⁸ These need to be addressed if safe discontinuation is to be performed routinely in clinical practice and not only in specialized centers.

Patients need to be willing to commit to the monitoring schedules recommended by physicians. Only approximately 50% of patients adhere to their monitoring schedule while on treatment.⁷⁰ To achieve a safe and successful TFR, compliant behavior requires reinforcement. Recently, a less frequent monitoring schedule model was proven safe.⁷¹ This might open the door to more physicians being able to offer TFR when they previously could not due to patients' financial constraints. A laxer approach might also be easier for patients and physicians to follow with better compliance results.

Conclusions

TFR is an attractive outcome that should be considered for appropriate patients for many different reasons, including QoL, long-term adverse effect avoidance, economic implications, and even as a possible operational cure. Regardless of these considerations, we must remember that TFR is not yet an outcome that applies to everyone. Roughly 75% of patients continue on treatment with currently available therapies. Only 50% are candidates to attempt TFR under ideal circumstances due to patient-related factors, CML response to treatment, and monitoring capacity. Of these, half maintain

Figure 1. Representation of patients who attempt and achieve TFR. Bosutinib and ponatinib are not included because there is no evidence of TFR with these TKIs. QoL and economic drivers may play a positive role in attempting TFR, whereas patient preferences might be positive or negative drivers. Other clinical considerations must be taken into account when deciding to attempt TFR.

Abbreviations: DMR, deep molecular response; QoL, quality of life; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

stable BCR-ABL transcripts without treatment reinitiation (Figure 1). There is definitely room for improvement so that more patients can benefit from this approach. Our focus, though, should remain maintaining next-to-normal OS with the least harm possible through our interventions. This opens the door to focusing on alternative treatment approaches for those unable to stop TKIs altogether, such as reduced TKI dosing as maintenance.^{33,72} This might prove to be an effective therapy with many of the benefits that TFR offers, including fewer dose-related adverse effects and appropriate disease control. This approach may apply to a wider population, but further research is needed before we are able to extend it to routine clinical practice.

TFR research is currently focusing on different strategies to increase the number of patients who can achieve successful discontinuation. A consolidative approach using more potent TKIs such as ponatinib after achieving DMR to further deepen responses (ClinicalTrials.gov identifier: NCT04043676), or using interferon maintenance after discontinuation (NCT03117816). The combination of medications such as interferons, ruxolitinib, or asciminib with TKIs to optimize responses (NCT02001818,

NCT01657604, NCT01872442, NCT03831776, NCT03610971, and NCT04216563) is another strategy used in many trials, both as initial therapy or after TFR attempts have been made. Before applying these strategies in clinical practice, trials will need to show further benefits to our current approach and increase eligibility for TFR, achieve successful and durable TFR, and improve QoL while remaining economically feasible. TFR might remain a desirable outcome for the near future but is not one that fits all patients.

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