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WJCO mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

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MINIREVIEWS

Predictive indicators of successful tyrosine kinase inhibitor discontinuation in patients with chronic myeloid leukemia

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Abstract

Clinical trials have demonstrated that some patients with chronic myeloid leukemia (CML) treated for several years with tyrosine kinase inhibitors (TKIs) who have maintained a molecular response can successfully discontinue treatment without relapsing. Treatment free remission (TFR) can be reached by approximately 50% of patients who discontinue. Despite having similar levels of deep molecular response and an identical duration of treatment, the factors that influence the successful discontinuation of CML patients remain to be determined. In this review we will explore the factors identified to date that can help predict whether a patient will successfully achieve TFR. We will also discuss the need for the identification of predictive biomarkers associated with a high probability of achieving TFR for the future personalized identification of patients who are suitable for the discontinuation of TKI treatment.

Key Words: Biomarkers; Tyrosine kinase inhibitors; Treatment discontinuation; Molecular monitoring; Duration of therapy; Leukemia; Myelogenous; Chronic; BCR-ABL positive

Core Tip: Clinical trials have shown that approximately 50% of patients with chronic myeloid leukemia who reach a deep molecular response (MR) following treatment for several years with tyrosine kinase inhibitors (TKI) can discontinue and remain in treatment-free remission (TFR). Factors such as the duration of TKI treatment and duration and depth of the patient's MR prior to discontinuation appear to be important in determining whether TFR is achieved. However, it is clear that other biological

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factors must determine whether an individual will remain in TFR after discontinuation. Future studies should aim to elucidate biomarkers predictive of TFR.

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INTRODUCTION

Chronic myeloid leukemia (CML) is a neoplasia of the pluripotent hematopoietic progenitor cells characterized by the clonal expansion of differentiated cells in the myeloid lineage[1] and classified by the World Health Organization within the group of chronic myeloproliferative neoplasms[2].

The constitutive activation of tyrosine kinases in hematopoietic stem cells is a common molecular basis of the myeloproliferative neoplasms. CML is defined by the presence of a reciprocal translocation between chromosomes 9 and 22 *t*(9; 22)(q34; q11), resulting in a shortened chromosome 22 known as the Philadelphia chromosome, which leads to the expression of the fusion oncogene *BCR-ABL1* encoding a constitutively active tyrosine kinase[3,4].

Imatinib mesylate (Gleevec®) was the first tyrosine kinase inhibitor (TKI) developed to target specifically the BCR-ABL1 oncoprotein. Physicians now have five approved TKIs available for the treatment of patients with CML: Imatinib (Gleevec®), dasatinib (Sprycel®), nilotinib (Tasigna®), and bosutinib (Bosulif®) for first- or second-line therapy and ponatinib (Iclusig) for patients with resistance or intolerance to prior therapy[4].

The outcome for CML patients has improved dramatically as a result of treatment with imatinib and other TKIs. In fact, most patient life expectancy is almost equivalent to that of the general population[5]. Despite their effectiveness in controlling the disease, TKIs are not considered to be curative, as they are not capable of eradicating the BCR-ABL1$^+$ leukemic stem cell. In fact, these cells do not depend on BCR-ABL1 for their survival and represent a reservoir capable of restoring CML, justifying the requirement for CML patients to take life-long daily oral TKI therapy[6-9].

However, recent clinical trials have demonstrated that approximately 50% of patients with CML treated for several years with TKIs and that reach a deep molecular response (MR) (DMR) (BCR-ABL1/ABL1 ≤ 0.01%, MR^4 or better) can successfully maintain remission after the discontinuation of TKI treatment, known as treatment free remission (TFR)[10]. Importantly, a 2017 survey determined that 81% of CML patients would be willing to attempt discontinuation[11].

Here, we will discuss which patients can discontinue TKI treatment and explore the factors that may predict whether a patient successfully achieves TFR.

Why discontinue TKI treatment?

One disadvantage associated with the use of these drugs is the development of side effects. Many patients experience mild to moderate non-hematologic TKI-related side effects, such as fatigue, nausea and vomiting, edema, diarrhea, headache, skin rash, muscle cramping, joint pain, night sweats, weakness, lack of appetite and myelosuppresion, especially when commencing TKI therapy. Indeed, only 60% of patients continue on the standard daily dose of 400 mg imatinib after 6 years due to intolerance or resistance[12], and approximately one-third of patients suffer moderate to severe TKI-related adverse effects[13] including neutropenia, thrombocytopenia and anemia.

In some cases, long-term treatment is associated with more serious off-targets despite not being reported in the initial clinical studies[14-16]. Such events comprise hepatic toxicity and coronary atherothrombotic, cerebrovascular and peripheral arterial events associated with nilotinib[17,18]; arterial and venous occlusive events with ponatinib[19,20]; pulmonary hypertension and pleural effusion with dasatinib use[21,22].

Adverse events can contribute to an impaired quality of life for patients with

CML[23,24], particularly for patients aged under 60 years, with the largest effects of TKI treatment on quality of life observed in patients aged 18-39 years[23]. Therefore, the successful discontinuation of TKI treatment would allow patients with CML to live a completely normal life.

Moreover, TKI treatment can affect fertility, and no TKI is recommended for women who wish to conceive or during pregnancy or lactation. Indeed, there is a higher tendency for women to interrupt TKI treatment than men[25]. Thus, the discontinuation of TKI therapy would allow women to have a normal pregnancy and be able to breastfeed.

Is TKI discontinuation feasible?

Various studies have demonstrated the viability of the discontinuation of TKI treatment[10]. As a result, TKI discontinuation has now become a feasible objective among clinicians in the management of patients with CML. For patients treated with imatinib, the STIM1 and STIM2 studies showed that a large proportion of patients with CML can benefit from the long-term suspension of TKIs (between 40% and 70% according to prognostic factors)[26,27]. In the case of patients treated with "newer" TKIs, such as nilotinib and dasatinib, recent clinical trials suggest a percentage of TFR equal or superior to trials with imatinib (see Table 1 for a non-exhaustive list of discontinuation trials). According to the results of studies in which our research group has participated, 52% of patients who discontinued nilotinib (ENESTFreedom) reached TFR[28], while for dasatinib (DASFREE) the TFR rate at 24 mo was 46%[29]. Interestingly, although clinical experience with the discontinuation of second-generation TKIs such as nilotinib and dasatinib is shorter, study results seem to indicate that the percentage of patients successfully achieving TFR will be higher than for imatinib and that a shorter duration of treatment may be needed prior to a discontinuation attempt[28,30,31].

All of these studies include the close monitoring of patients (monthly BCR-ABL1 transcript determinations during the first 12 mo), with the aim of detecting the signs of relapse as soon as possible. Importantly, practically all the patients who did relapse after discontinuation responded well to re-treatment[26,27]. Moreover, a meta-analysis of discontinuation studies determined that the suspension of imatinib neither increased the probability of disease progression nor the risk of death, with all CML patients alive after 2-year follow-up (only one patient had progressed to blast crisis, 0.8%)[32].

Prognostic variables for TFR

To date, the variables shown to be predictive of a higher probability of TFR success are those related with CML characteristics and TKI treatment, such as the Sokal score, duration of TKI treatment, and duration and depth of MR[10].

Sokal score: The percentage of patients with a low, intermediate or high Sokal score who achieved TFR in the TWISTER study was 51%, 37% and 25%, respectively[33]. Likewise, patients with a low or intermediate Sokal score who discontinued imatinib in the STIM1 study were found to have a higher probability of obtaining TFR[26].

Duration of TKI treatment: Results from the STIM1 study also revealed a higher probability of obtaining TFR for patients who had received more than 4.5 years of TKI therapy[26]. This observation was confirmed by the KID study and the EURO-SKI study, the latter of which revealed that patients who had reached at least a MR^4 during 1 year and had received TKI treatment for longer than 5.8 years had a higher TFR rate than those who had received imatinib for less than 5.8 years (65% *vs* 42.6%, respectively)[34-36]. Moreover, according to European Society for Medical Oncology (ESMO), the "stability of TFR is improved with longer TKI therapy and longer DMR"[37]. Of note, the DASFREE study reported a TFR at 12 mo of 54% for patients who discontinued dasatinib as first-line TKI treatment compared to a TFR of 43% for patients who discontinued dasatinib in the second-line. Moreover, no significant association was found between TFR and duration of prior TKI therapy[29]. This result suggests that first-line treatment with second generation TKIs may help improve the probability of reaching TFR.

Duration and depth of MR: Results from several studies have revealed a positive association between the level (or depth) of molecular response and the probability of TFR success. For example, the Japanese STAT2 trial found that the TFR rate after 36 mo was significantly higher in patients with undetectable molecular residual disease than in patients without (76.6% *vs* 48.6%, respectively)[38]. This finding was confirmed by the JALSG-STIM213 study, which discontinued CML patients who had received imatinib for at least 3 years and had a sustained DMR for at least 2 years, and reported

Table 1 Summary of level (depth) of molecular response required prior to discontinuation attempt in discontinuation clinical trials, for all of these studies, molecular relapse was considered to be loss of major molecular response

Molecular response	Trial	TKI	TFR, %	TFR at month
MMR	Destiny	Dasatinib	39	24
DMR	JALSG-STIM213	Imatinib	68	12
DMR	DASFREE	Dasatinib	63	12
DMR	ENESTFreedom	Nilotinib	52	12
DMR	ENESTop	Nilotinib	58	12
DMR	EURO-SKI	Mixed	61	6
CMR[1]	STIM1[2]	Imatinib	43	6
UMRD	ISAV[3]	Imatinib	48	36
UMRD	STOP 2G-TKI[4]	Mixed	61	12
UMRD	STIM2[5]	Imatinib	64	6
UMRD	KIDS[6]	Imatinib	62	12
UMRD	TWISTER[6]	Imatinib	47	24

[1]Complete molecular response should not be detectable but could be MR^4 or $MR^{4.5}$ depending on the sensitivity of the BCR-ABL1 transcript quantification technique used[63].
[2]> 5-log reduction.
[3]Limit of detection log4-4.5.
[4]Undetectable BCR-ABL1 by real-time quantitative polymerase chain reaction, with at least 20,000 copies of the control gene.
[5]Undetectable BCR-ABL1 with sensitivity ≥ 50000 amplified copies of *ABL1* control gene.
[6]Limit of detection log4.5. CMR: Complete molecular response; DMR: Deep molecular response MR^4 or better (< 0.01%); MMR: Major molecular response, MR^3 (0.1%); TFR: Treatment free remission; TKI: Tyrosine kinase inhibitor; UMRD: Undetectable molecular residual disease.

a TFR rate of 72% after 3 years for patients with undetectable molecular residual disease (UMRD) compared to 35.7% for patients with $MR^{4.5}$ prior to discontinuation[39]. This association was also indicated by the ISAV study, which employed digital polymerase chain reaction (dPCR) to predict relapses after imatinib discontinuation in CML patients who had maintained complete molecular response (CMR) (defined as undetectable BCR-ABL1 transcripts by quantitative PCR, with a limit of detection of 4–4.5 Logs) during at least 18 mo. The study reported a TFR rate at 36 mo of 48% and although no association was found between the risk of molecular relapse and Sokal score, duration of imatinib treatment, or duration of CMR–dPCR positivity was significantly associated with relapse[40]. Finally, the analysis of data from the EURO-SKI study suggested that a longer duration of deep molecular response was positively associated with TFR[35,37].

The predictive value of these variables was confirmed by two recent meta-analyses that collectively considered 22 TKI discontinuation studies comprising 3300 chronic myeloid leukemia patients and concluded that depth of molecular response trials[41] (specifically trials whose eligibility criteria required $MR^{4.5}$ or better prior to discontinuation[42]) and duration of DMR[41] (specifically trials that required at least 24 mo of DMR[42]) were associated with higher TFR rates.

Imatinib resistance: One important result from the STOP 2G-TKI study was that resistance to imatinib or poor response was associated with a significantly lower probability of achieving TFR after TKI discontinuation[30].

Nevertheless, it is difficult to compare the results of many discontinuation studies due to the different criteria used in each case, in terms of the length of TKI treatment as well as the level and duration of molecular response required prior to discontinuation. Even the definition of molecular relapse varies considerably from study to study, depending on the criteria of each clinical trial (Table 1). For example, prior to TKI discontinuation, DMR was required by the DASFREE[29], EURO-SKI[36] and ENESTFreedom[28] studies; whereas the KIDS[34] and TWISTER[33] studies required a depth of MR as stringent as UMRD.

As a consequence of these findings on variables that are predictive of TFR success (and many others that have not been named in this review due to space restrictions),

both the United States National Comprehensive Cancer Network (NCCN) and the ESMO developed guidelines for the safe discontinuation of TKI treatment for patients with CML[37,43]. The criteria for patient selection for a discontinuation attempt according to the NCCN guidelines from 2018 include TKI treatment for at least 3 years and a maintained MR^4 or above for at least 2 years, as well as no history of TKI resistance[43]. The 2017 ESMO guidelines also require a maintained DMR for at least 2 years but require at least 5 years of TKI therapy prior to the discontinuation attempt and the achievement of $MR^{4.5}$[37].

Real-life discontinuation studies

As previously discussed, numerous clinical trials have endeavored to establish criteria for the safe discontinuation of TKI treatment in patients with CML. Although the evidence related to the applicability of such criteria to clinical practice is limited, several groups have attempted to evaluate the safety of TKI discontinuation outside of controlled trials.

The Spanish Group on CML (GELMC) analyzed a series of 236 discontinued patients from 33 national centers and reported that 164 patients maintained a major molecular response (MMR) after a median follow-up of 21.5 mo, while 67 patients (28%) had to reinitiate TKI treatment due to loss of MMR (at two consecutive controls with an increase > 1 Log of BCR-ABL1). The probability of reaching TFR at 12 and 48 mo was 72.5% and 64%, respectively[44]. A similar observational study of 293 Italian patients who discontinued TKI, with a median follow-up of 34 mo, reported that 39% had to reinitiate treatment, due to loss of MR^4 (19%), loss of MMR (70%) or loss of cytogenetic response (9%). Moreover, a multivariate analysis revealed that the discontinuation of second-generation TKIs (28% of patients) had superior TFR rates than imatinib (73% *vs* 68% at 12 mo, respectively)[45]. Finally, the study conducted at the MD Anderson Cancer Center on 100 patients who had reached $MR^{4.5}$ prior to discontinuation reported a TFR rate of 70% at 2 years, and determined that patients with a duration of $MR^{4.5}$ of 2 years had a probability of losing MMR of 29% compared to only 7% for patients with a duration of $MR^{4.5}$ of 6 years[46].

Together, the results of these real-life studies confirm that the discontinuation of TKI treatment in clinical practice is viable and safe for many CML patients. It is important to note that they also support the duration of TKI treatment and particularly the duration of DMR prior to discontinuation as clinical variables that are positively associated with TFR.

Selection of patients for TKI discontinuation

Although the seminal discontinuation studies of imatinib (EURO-SKI) commenced in 2010, and those for nilotinib (ENESTFreedom) and dasatanib (DASFREE) in 2013, there is still no European or international consensus regarding what criteria are important for selecting patients for a discontinuation attempt. Despite this (and although discontinuation of TKI therapy is still largely conducted in controlled clinical trials), our hospital, in collaboration with the Canarian CML Group, has developed a standard protocol for TKI discontinuation in clinical practice based on the current NCCN[43] and ESMO guidelines for the selection of CML patients for TKI discontinuation[37].

To be eligible for consideration for TKI discontinuation at our center or other hospital in the Canary Islands, CML patients must meet the criteria as set out in the "TKI Treatment Discontinuation in Patients with Chronic-phase CML"–Canarian CML Group protocol (Table 2), which has the aim of assuring the maximum rate of discontinuation success.

The importance of molecular factors for the prediction of TFR

There is a real clinical need to study CML patients who successfully achieve TFR and those who suffer molecular relapse in order to identify the molecular factors that have a significant role in remission. Such molecular factors could potentially be used as biomarkers to predict which patients are likely to reach TFR. The identification of predictive factors for TFR in CML will also help define criteria for safer discontinuation attempts with a greater probability of success.

Although the global duration and other variables related to TKI treatment prior to discontinuation are associated with TFR[10,41,42], it is clear that other biological factors must exist that determine whether an individual will or will not remain in TFR when the TKI is withdrawn. To date, very few studies have investigated this at the molecular level, although some suggest a possible role of the immune system[35]. For example, a maintained TFR following the discontinuation of imatinib was associated with high

Table 2 Inclusion and exclusion criteria for patient selection from the Canarian-chronic myeloid leukemia "Tyrosine kinase inhibitor treatment discontinuation in patients with chronic-phase chronic myeloid leukemia" protocol

Inclusion criteria, all should be met	Exclusion criteria
Aged 18 yr or over, with diagnosis of CML in chronic phase	Resistance to any TKI or insufficient response to imatinib
Received 5 yr or more of TKI treatment (imatinib, bosutinib, nilotinib or dasatinib)	Accelerated phase or blastic crisis in any moment
Maintained a $MR^{4.5}$ (BCR-ABL1/ABL1 < 0.0032%) or better in all samples taken during the last 3 yr (with at least one recent sample certified in a centralized laboratory)	Detection of BCR-ABL1 kinase domain mutations in any moment
Present a typical BCR-ABL1 transcript at diagnosis that permits quantifiable molecular monitoring	
A low or intermediate Sokal index at diagnosis	
Give written informed consent	

CML: Chronic myeloid leukemia; MR: Molecular response; TKI: Tyrosine kinase inhibitor.

levels of NK cells[47-50], increased CD3(+)CD8(+)CD62L(+) T cells[48], increased expression of CD56 and NKG2D in NK cells and lower expression of CD86[51].

Interestingly, Caocci *et al*[52] recently described an association between the presence of specific polymorphisms of the killer immunoglobulin-like receptor (KIR) and TFR[52]. The authors analyzed 36 CML patients with a $MR^{4.5}$ and observed that after discontinuation, those with the homozygotic haplotype KIR A/A had a significantly higher TFR than those with haplotype B/x. These results suggest that specific mutations may cause an increased expression of tumoral antigens and thus change the vulnerability of the tumor cells to the immune system. However, these results did not coincide with those of the EURO-SKI study, in which the authors observed no differences in TFR in relation to KIR haplotype[35].

To the best of our knowledge, only one preliminary study has specifically searched for mutations in CML patients who achieved TFR using exome sequencing[53]. The study compared the exome sequence of three patients who achieved TFR with three patients who relapsed after TKI discontinuation and identified a variant in *PARP9* in the TFR group and variants in *CYP1B1, ALPK2* and *IRF1* in the relapsed group[53]. Although only a small number of patients' exomes were sequenced, making the formation of scientific conclusions difficult, the study demonstrates that the existence of variants in genes of diverse functions may contribute to the maintenance of TFR.

Other intriguing results have linked high miR-126 levels with higher numbers of quiescent CML stem cells[54]. Therefore, it would be interesting for future studies to analyze the role of the expression of certain microRNAs with the successful obtention of TFR.

FUTURE RESEARCH DIRECTIONS

Need to determine molecular factors associated with TFR

As mentioned above, there is a real need to identify molecular factors associated with TFR to identify patients with CML with a higher probability of reaching TFR. Studies indicate that the incidence of deep molecular responses, a prerequisite for TFR in many studies and one of the patient selection criteria according to the ESMO 2017 guidelines, is quite low. For example, in the IRIS[55], DASISION[21] and ENESTnd[56] studies, the $MR^{4.5}$ rates after 5 years of TKI treatment were 23.3%, 33% and 31%, respectively. As such, current patient selection criteria may be overly restrictive and thus limit the number of patients who can currently make a discontinuation attempt.

In addition, the identification of molecular factors predictive of TFR would bring substantial savings for national health systems. The current price of TKI treatment in most European countries is approximately 2500–3500 € *per* month[10], although this is substantially reduced in the case of generic imatinib (approximately 100 € *per* month). In actual fact, the savings would be even greater, since the health system would not have to treat the appearance of adverse effects often associated with TKI treatment, including serious cardiovascular comorbidities. CML has an incidence of 1–1.5 cases per 100000 inhabitants per year and the average age of patients presenting with CML is 60–65 years. Thus, these potential savings could become critical in the future for

national health systems due to the increased aging of the global population[57], which will result in an estimated 35-fold rise in incidence of CML, with a peak in prevalence around the year 2050[58].

Influence of second discontinuation attempt

The evidence to support the safety and viability of a second discontinuation attempt in patients with CML who lost molecular response in a first discontinuation attempt is scarce. The prospective RE-STIM study reported the second discontinuation attempt of 70 patients with TFR rates at 12 and 24 mo of 48% and 42%, respectively[59]. Importantly, no patient progressed toward advanced-phase CML and 76% of patients regained at least a $MR^{4.5}$ with a median of 6.5 mo, while 18% regained MMR with a median of 4.6 mo. The treatment-free remission accomplished by dasatinib (TRAD) study aimed to determine whether patients could reach TFR in a second discontinuation attempt after failing a first discontinuation attempt with imatinib and re-initiating treatment with dasatinib. However, the preliminary second discontinuation results were disappointing, with 84% of patients losing molecular response after a median of 3.7 mo[60]. However, these data argue in favor of the safety of a second discontinuation attempt.

Since the molecular factors associated with TFR are yet to be determined for a first discontinuation attempt, it is too early to indicate possible factors that may influence the success of a second TKI discontinuation attempt. Nevertheless, analysis of RE-STIM data revealed that for patients who had remained in DMR within the first 3 mo upon TKI re-initiation following a first unsuccessful TKI discontinuation attempt, the TFR rate at 24 mo was 72% compared to 36% who did not[59]. Also, results from the TRAD study suggested that one additional month of first TFR duration correlated with a 51.5% reduced risk of molecular relapse in the second discontinuation attempt[60].

Patient perspective

It is important that medical practitioners consider the patient's psychological and emotional factors, in addition to clinical variables, when selecting patients for discontinuation. The discontinuation of TKI treatment should have a positive effect on patient quality of life, which should be the primary objective of any discontinuation attempt.

Clinicians should inform patients of the possible disadvantages of a discontinuation attempt. For example, during the first years following TKI cessation, and particularly during the first 12 mo, patients are required to undertake more frequent molecular monitoring to detect possible loss of MR as soon as possible, meaning more blood tests and visits to the clinician. For example, patients in maintained DMR undergo controls every 3 or 6 mo, whereas for patients who discontinue TKI treatment, the controls are monthly for the first year, every 6–8 wk for the following 6 mo, and every trimester from 18 mo onwards. Moreover, approximately 30% of patients may experience temporary TKI withdrawal side effects, particularly during the first weeks after TKI suspension, such as musculoskeletal pain[61].

Indeed, there is a real need for quality of life analysis since current discontinuation guidelines do not address the psychological issues related to discontinuing TKI therapy and attempting TFR, such as the fear of disease recurrence or progression[62]. Studies are required that monitor the physical and psychological impact of discontinuation on the quality of life of patients who discontinue TKI treatment using a standardized and accredited questionnaire, such as the "Change of Health-related Profiles after Imatinib Cessation in Chronic Phase Chronic Myeloid Leukemia Patients" validated questionnaire[63], to help determine emotional characteristics that should be included in the eligibility criteria for patients and thus help refine criteria for future discontinuation attempts. Similarly, very little information exists on the impact on quality of life of patients treated with second-generation TKIs. It is a possibility that those patients with a higher incidence of adverse effects would be more willing to attempt discontinuation[62] and that experiencing certain adverse effects could even be a factor in reaching TFR. For example, among patients with the myeloproliferative neoplasm essential thrombocythemia, the manifestation of pruritus, a common side effect for this neoplasia, was associated with a more proliferative and aggressive form of the disease[64].

CONCLUSION

To date, clinical trials and real-life discontinuation studies have confirmed the viability

and safety of the discontinuation of TKI treatment in the majority of patients with CML who undergo such an attempt. However, the current selection criteria for TKI discontinuation, as recommended by the NCCN and ELN guidelines, are quite restrictive and so the number of eligible CML patients are limited.

The identification of predictive factors for TFR in CML will inform the clinic on the best candidates to include in future discontinuation attempts and will help define criteria for safer discontinuation attempts with a greater probability of success. Moreover, it would potentially give more patients a chance at stopping TKI treatment. The identification of CML patients with a higher probability of achieving TFR after TKI discontinuation would bring with it substantial savings for national health systems. At present, TKI treatment costs approximately 30000-45000 € per year per patient in most European countries, although this is substantially reduced in the case of generic imatinib. Indeed, the saving would be even greater, since the health system would not have to treat the appearance of adverse effects often associated with TKI treatment, including important cardiovascular comorbidities, hepatic toxicity, or pleural effusion.

Current predictive indicators of the maintenance of TFR include factors related to the duration of TKI treatment and the duration and depth of the patient's MR prior to discontinuation. Some immune factors also appear to be important in determining whether TKI discontinuation is successful.

However, future studies are required to elucidate biomarkers predictive of TFR after discontinuing TKI treatment. Besides increasing our understanding of the underlying molecular mechanisms of this pathology, such studies would help refine the discontinuation criteria and may identify novel prospective therapeutic targets for CML. Thus, the determination of the molecular factors that influence TFR would be a significant advancement in personalized medicine.

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