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LEUKEMIA (A AGUAYO, SECTION EDITOR)

Current Information and Recommendations on the Discontinuation of TKI Inhibitors in Chronic Myeloid Leukemia

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Abstract

Purpose of Review Discontinuation of tyrosine kinase inhibitors (TKIs) in chronic phase chronic myeloid leukemia (CP-CML) patients has become a reality. Treatment-free remission (TFR) is the term that identifies success after discontinuation.

Recent Findings Several trials have demonstrated that with imatinib about 40% of patients discontinuing treatment in deep and stable molecular response remain disease-free. Second-generation TKIs have improved the rate of deep molecular responses and allowed to increase the percentage of patients attempting treatment discontinuation.

Summary We hereby review the current information based on the available published data and discuss the current suggestions on how to move TFR into the clinical practice.

Keywords Chronic myeloid leukemia · Tyrosine kinase inhibitors · Discontinuation · Treatment-free remission

Introduction

Imatinib has dramatically impacted on the management of chronic myeloid leukemia (CML) allowing to obtain more than 80% of complete cytogenetic responses (CCyR) and long-term overall survival (OS) rates greater than 90%, considering only CML-related deaths [1••]. However, deep molecular responses, measured by reductions of BCR-ABL transcript levels below the threshold of major molecular response (MMR, ratio BCR-ABL/ABL < 0.1% according to the International Scale (IS)) are achieved only by a small proportion of patients [2]. The frontline use of the second-generation tyrosine kinase inhibitors (TKIs) nilotinib and dasatinib in newly diagnosed patients has increased the proportion of patients achieving very deep and stable molecular responses [3•, 4•]. New cut-offs of molecular residual disease have been defined following the introduction of more potent and selective TKIs as frontline treatment: MR4, corresponding to a BCR-ABL ratio < 0.01%, MR4.5, corresponding to a ratio < 0.0032%, and MR5, corresponding to a 5-log reduction or < 0.001% according to the IS [5••].

In 2006, John Goldman introduced in the clinical practice the clinical definition of "operational cure" [6] following the observation that some patients after an allogeneic stem cell transplant or interferon therapy could discontinue treatment. In these patients, molecular monitoring by RQ-PCR demonstrated the persistence of residual disease, that however did not require to restart treatment. This observation then translated into the era of TKIs: the term "treatment-free remission" (TFR) indicates the possibility of remaining without treatment after the achievement of a stable and deep long-lasting molecular response [7].

Aim of this review is to report and analyze the results of the different published discontinuation studies and to discuss the recommendations on how to optimally define potential candidates to TFR, the new endpoint in the management of CML patients.

Imatinib Discontinuation Trials

The first pilot study was reported by the French group, which tested the discontinuation of imatinib in 12 CML patients with undetectable molecular disease lasting for more than 2 years. Molecular relapse was defined as RQ-PCR positivity

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confirmed in two consecutive samples. All but two patients had been pre-treated with interferon for a median of 33 months, whereas the median time of imatinib treatment was 45 months. Molecular relapse occurred in six patients (50%) within the first 5 months, but all were successfully retreated. Owing to the few patients enrolled, the group did not identify predictive prognostic factors for relapse, except for a trend for a shorter time to RQ-PCR negativity in non-relapsing patients [8].

The STIM1 study was a prospective trial in which 100 CP-CML patients with undetectable molecular disease (defined as a 5-log reduction) for more than 2 years after imatinib treatment were enrolled. Fifty-one percent of patients had been previously exposed to interferon. Molecular relapse was defined as two positive RQ-PCR controls 1 month apart with a significant rise of 1-log in the BCR-ABL transcript. At the last reported follow-up of 77 months, 61 of the 100 patients had relapsed; 58 of them were early relapses occurring during the first 7 months of discontinuation and 3 were late relapses, with no relapses observed after the second year. The cumulative incidence of relapse was estimated to be about 60%. During the discontinuation period, five deaths occurred for CML non-related causes. All relapsed patients were successfully retreated (48 patients with imatinib and 10 patients with a second-generation TKI) and all regained a molecular response: no patient developed mutations of kinase domains or progressed to an advanced phase of the disease. An initial sub-analysis performed to identify prognostic features predictive for stable complete molecular response (CMR) after imatinib discontinuation showed that a low Sokal risk and a long treatment duration prior to discontinuation were two independent factors associated with a low rate of molecular relapse [9••].

The prospective TWISTER study was the second example of discontinuation trial carried out by the Australian group: 40 CML patients with undetectable molecular disease (MR4.5) lasting for more than 2 years after a minimum of 36 months of imatinib treatment were enrolled. Molecular relapse was defined as any single sample with loss of MMR (ratio > 0.1%) or two consecutive positive samples of any value confirming the loss of undetectable response. Again, as in the STIM1 study, 21 patients had been previously pre-treated with interferon. At 24 months, the estimated rate of TFR was 42.7%, with the majority of relapses occurring in the first 6 months and seven as late relapses that occurred between 6 and 27 months. A different behavior was observed in relapsed patients: the median fold-rise of the transcript level in patients with earlier relapses was 91.5 with a median BCR-ABL doubling time of 12.8 days, whereas the median fold-rise was 3.3 in patients with late relapses with a median doubling time of 72.2 days. The rechallenge with the same drug was successful in all patients. The relapse risk was significantly associated with a shorter duration of the previous IFN treatment, time to achieve undetectable disease after switching from IFN to imatinib and a high Sokal risk. Patient-specific PCR based on DNA was tested in this trial: this tool demonstrated the persistence of the original CML clone in all patients with stable molecular response, even after several years from imatinib discontinuation [10].

The KIDS multicenter prospective Korean discontinuation study enrolled a total of 48 patients on treatment with imatinib for more than 3 years who had an undetectable molecular response for at least 2 years. Twenty patients had previously received an allogeneic transplant and were treated with imatinib after relapse. Endpoints were the probability of a sustained UMRD (undetectable response) and MMR at 12 months after discontinuation, and the identification of factors predictive of a sustained molecular response. Relapse was considered as the loss of MMR. After a median follow-up of 26.6 months, 37 patients lost the MMR with a probability of maintaining a MR3 at 24 months of 58.5%. All patients who restarted imatinib after relapse obtained again a MR3 after a median of 3.9 months. Long-term duration of imatinib treatment and the occurrence of musculoskeletal pain, known as "whitdrawal syndrome" were associated with a sustained MR3 after discontinuation [11].

The French group reported an analysis on 80 patients who were included in the so-called "According to STIM" experience: patients were enrolled if they had achieved a MR4.5 or an undetectable disease for at least 2 years. The criterion to define a molecular relapse was the loss of MMR; using this endpoint, after a median follow-up of 36 months, 61% of patients remained treatment-free. Previous IFN therapy seemed to prolong the treatment-free survival. A fluctuation of the molecular levels above 0.1% IS without relapse and need to restart treatment was demonstrated in 31% of patients [12•].

After the first STIM1 study, further studies have been reported following treatment with imatinib. These include STIM2 [13] which enrolled only patients treated with imatinib first-line (without previous exposure to IFN) and the Japanese study STIM213, which reported a TFR at 12 months of 69.1% in patients treated with imatinib for more than 3 years and in stable MR4.5 for almost 2 years [14]. An Italian study (ISAV) enrolled 112 patients treated with imatinib, even after previous IFN exposure, who discontinued treatment when in MR4.5 and considering as relapse the loss of MR3. A molecular relapse was experienced by 50.9% of patients, the majority occurring during the first 9 months (70.9%). Two patients were described as having a late relapse after 30.5 and 45.5 months. Fifty-three patients experienced a fluctuation of molecular residual disease without losing MR3. No correlations were found in this study between occurrence of relapse and median time of treatment, median time of deep MR, previous IFN exposure and Sokal risk. An inverse correlation between age and risk of relapse was shown, with an increased risk in patients aged less than 45 years. Digital PCR was tested in this trial and a significant predictive value with early relapses was reported [15]. A retrospective Italian study showed the

outcome of patients after discontinuation performed outside of clinical trials because of toxicity, pregnancy or other reasons. Two hundred and eight patients were collected in 23 different institutions, median age was 59 years, with 13% of patients having a high Sokal risk. Eighty-one percent of patients were treated frontline (74% with imatinib) with a median duration of CMR before discontinuation of 23 months. The TFR at 28 months was 59.3%. In multivariate analysis, predictive factors associated to an increased risk of relapse were younger age and depth of response at the time of discontinuation [16] (Table 1).

The EURO-SKI Study

A large European study was conducted supported by the EUTOS group. Patients were allowed to enter if on treatment with all available TKIs for more than 3 years and in stable MR4 for more than 1 year. After a confirmation of MR4 during an initial screening phase, patients who discontinued were monitored every month for the first 6 months, then every 6 weeks up to the end of the first year and thereafter every 3 months. Seven hundred and fifty patients were analyzed; 18% of them had a high Sokal risk at presentation. The median age was 52 years, whereas the median duration of treatment was 7.7 years and the median duration of MR4 before treatment discontinuation was 4.7 years. Ninety-four percent of patients were treated with imatinib, 2% with dasatinib, and 4% with nilotinib. The molecular relapse-free survival at 36 months was 50%, with 413 patients remaining in MR3 at the last follow-up. Univariate analysis of prognostic factors associated with a molecular relapse-free survival (RFS) at 6 months showed that age, gender, depth of molecular response, or any initial stratification (Sokal, EUTOS or ELTS score) were not predictive. Indeed, treatment duration with imatinib and MR4 duration had similar odds ratio of 1:16, which means that any additional year of imatinib treatment increases the likelihood of remaining in MR3 at 6 months by 16%. A cut-off of imatinib treatment duration > 5.8 years and of MR4 duration > 3.1 years before attempting discontinuation were found. None of the patients who lost the MR3 progressed or died from the disease and 72 patients had an increased ratio > 1%. More than 80% of patients who restarted treatment after relapse regained a MR4. A saving of 27 millions of euro was estimated [17•]. A sub-analysis of the study evaluated the molecular RFS according to the level of molecular response at the time of discontinuation: no differences were detected for patients in MR4 who never achieved a MR4.5 (RFS 61%) compared to detectable MR4.5 (51%) or undetectable MR4.5 (62%) [18]. A subsequent analysis reported also the differences between detectable and undetectable MR4 without differences in molecular RFS [19].

Table 1 Overview of imatinib discontinuation trials

Study	No. of pts	Treatment	Response required at study entry	Relapse threshold	Median duration of therapy at study entry	TFR outcome
STIM1	100	Imatinib (1st line or after IFN)	> MR4.5 (undetectable transcript for at least 2 years)	Loss of CMR or increase of > 1 log	> 3 years	39% at 77 months
TWISTER	40	Imatinib (1st line or after IFN)	MR4.5 (undetectable transcript for at least 2 years)	Loss of confirmed MR4.5 or MMR	> 3 years	42.7% at 24 months
A-STIM	80	Imatinib (1st line or after IFN)	MR4.5 for at least 2 years	Loss of MMR	> 3 years	61% at 36 months
KIDS	90	Imatinib (1st line or after IFN)	MR4.5 (undetectable transcript for at least 2 years)	Loss of MMR	> 3 years	58.5% at 24 months
ISAV	108	Imatinib (1st line or after IFN)	MR4 or 4.5 (undetectable transcript for at least 18 months)	Loss of MMR	> 3 years	50.9% at 45 months
STIM2	124	Imatinib (1st line)	> MR4.5 (undetectable transcript for at least 2 years)	Positivity of RQ-PCR confirmed indicating increase of one log or loss of MMR at one point.	> 3 years	61% at 1 year
STIM213	77	Imatinib (1st line or after IFN)	MR4 for more than 24 months confirmed on 4 tests	Loss of MMR	> 3 years	67.6% at 1 year
EUROSKI	750	Imatinib (1st line or after IFN) and dasatinib or nilotinib	MR4 for at least 1 year	Loss of MMR	> 3 years	50% at 36 months

First Examples of Second-Generation TKI Discontinuation Trials

STOP second-generation TKIs was the first example of discontinuation of dasatinib and nilotinib performed by the French CML group. Patients enrolled were treated with second-generation TKIs for more than 3 years as second line after resistance and/or intolerance to imatinib, and who were in undetectable response after more than 24 months. The primary endpoint was to establish survival without loss of MMR, which defined the criterion for molecular relapse and for resumption of therapy. Sixty patients who discontinued treatment were reported (30 treated with nilotinib and 30 with dasatinib); only 13% of them had a high Sokal risk at presentation, 67% were intolerant to imatinib. Only 10% were treated frontline. After a minimum follow-up for all patients of 12 months, the probability of remaining in stable MMR was 63.3%. No progressions to advanced phase of the disease were recorded. Analysis of variables associated to stable MMR showed that suboptimal response or treatment failure were associated with a high probability of relapse, but the analysis was impaired due to the small sample size. The majority of patients relapsed before 12 months of discontinuation (21 patients) and only five after 12 months [20].

The Japanese group reported the results of the DADI trial in which 63 patients were treated second line with dasatinib: to be enrolled, patients were required to have a molecular response < 0.0069% maintained for more than 1 year and the relapse was defined as the loss of MR4. Again, the majority of relapses occurred in the first 7 months from discontinuation and the probability of TFR at 12 months was 48%. All patients regained response after rechallenge with the same drug or with nilotinib (one patient). An increased probability of maintaining a TFR was observed in patients intolerant to imatinib (65%) rather than resistant (10%) [21] (Table 2).

Dose De-escalation as a Strategy for TFR

The UK group reported the feasibility of treatment de-escalation rather than outright cessation and the effect of discontinuation in patients in MR3 who never achieved MR4 in the phase 2 DESTINY trial. Patients were enrolled if they had received the TKI for more than 3 years and were in stable MR4 or in stable MR3 but not MR4 lasting for more than 12 months. Patients were treated with half standard dose: imatinib 200 mg daily, dasatinib 50 mg daily, or nilotinib 200 mg twice daily for 12 months. Relapse was considered as the loss of MR3 on two consecutive samples and the primary endpoint was to establish the proportion of patients who lost MR3 after de-escalation strategy. One hundred and seventy-four patients were enrolled, 49 in the MR3 cohort, and 125 in the MR4 cohort. During the de-escalation phase, 12 patients experienced a recurrence of disease. Only 2% of patients relapsed in the MR4 cohort compared to 19% in the MR3 cohort, regardless of the type of TKI. Loss of response was not associated with age, gender, performance status, prior TKI or duration of response [22]. The last follow-up at 24 months showed a TFR of 78% for the MR4 cohort and of less than 40% for the MR3 cohort. The probability of TFR for the MR4 cohort was higher if compared to patients enrolled in the EURO-SKI trial [23].

TFR Studies Involving Nilotinib

The ENESTFreedom study is the first prospective, phase 2, single-arm study that evaluated the discontinuation of nilotinib as first-line treatment. The trial enrolled CP patients treated with frontline nilotinib for > 2 years and in sustained MR4.5 for more than 1 year. Patients had to restart treatment after the loss of MR3. Overall, 215 patients entered the consolidation phase and 190 were enrolled in the TFR phase. The median duration of nilotinib prior to TFR was 43.5 months and the median time from the first MR4.5 to TFR entry was 30.4 months. Median age at study entry was 55 years (range 21–86) and 28 patients were stratified as having a high Sokal risk. At 96 weeks, the TFR was estimated to be 48.9%, because 93 of the 190 patients remained off treatment and in MR3; 88 patients had a sustained MR4.5. Compared to the last follow-up reported of 48 weeks, five patients were no longer in TFR, three because they lost MR3 after 48 weeks, and two because they discontinued the study without loss of MR3. The estimated rate of treatment-free survival at 96 weeks was 50.9%. Of the 88 patients who reinitiated nilotinib due to loss of MR3, 87 (98.9%) regained MR3 and 81 (92%) regained MR4.5. A sub-analysis was conducted that showed that the TFR rate at 48 weeks was different according to the Sokal risk at baseline (62.9, 50, and 32.1% for low, intermediate, and high risk, respectively) and the BCR-ABL1 level in the consolidation phase (52.9% for patients who persisted with a transcript level < 0.0032% in all assessments and 40% for patients with a transcript level > 0.0032% in ≥ 1 assessment). Overall, eight deaths were reported and two of them were for cardiac reasons (one in consolidation phase and one in reinitiation phase). Musculoskeletal pain was reported as a side effect at discontinuation in 34% of patients in the first 48 weeks and decreased to 9% in the subsequent 48 weeks, as also the incidence of other adverse events [24•].

Nilotinib was also tested as second-line treatment in the ENESTop study that enrolled patients treated with imatinib for more than 3 years with detectable molecular response who switched to nilotinib for more than 2 years and discontinued when a stable MR4.5 was reached. One hundred and twenty-six patients entered the TFR phase, median age was 56 years (range 21–86) and they were treated for a median

Table 2 Overview of second generation TKIs discontinuation trials

Study	No. of pts	Treatment	Response required at study entry	Relapse threshold	Median duration of therapy at study entry	TFR outcome
STOP 2G TKI	60	Nilotinib (30 pts) or dasatinib (30 pts) second line	> MR4.5 (undetectable transcript for at least 2 years)	Loss of MMR	> 3 years after resistance/ intolerance to imatinib	63.3% at 1 year
DADI	63	Dasatinib second line	BCR/ABL1 ratio < 0.0069% for at least 1 year	Loss of MR4	> 3 years	48% at 1 year
D-STOP	65	Dasatinib as consolidation for 2 years	MR4 for at least 2 years	Loss of confirmed MR4	> 3 years	62.9% at 1 year
DASFree	90	Dasatinib 1st or 2nd line	MR4.5 (undetectable transcript for at least 1 year)	Loss of MMR	> 2 years	63% at 1 year
ENESTFreedom	190	Nilotinib 1st line	MR4.5 (undetectable transcript for at least 2 years)	Loss of MMR	> 2 years	48.9% at 96 weeks
ENESTop	126	Nilotinib 2nd line	MR4.5 (undetectable transcript for at least 2 years)	Loss of MR4 or confirmed loss of MR3	> 2 years	53.2% at 96 weeks

of 77.9 months with imatinib followed by nilotinib. The median exposure to nilotinib was 53 months. At 96 weeks from the start of the TFR phase, 67 of the 126 patients (53.2%) remained in TFR (relapse threshold considered as the loss of MR4 or confirmed loss of MR3). Between 48 and 96 weeks, 73 patients were considered non-responders: of them, 4 for a confirmed loss of MR4 and 2 patients who discontinued for a pregnancy and for the patient's decision. Of 56 patients who reinitiated nilotinib, 52 (92.9%) regained MR4 and MR4.5 in a median time of 12 and 13 months, respectively. Musculoskeletal pain occurred in 47.9% of patients during the first 48 weeks and in 15% of patients in the second period, between 48 and 96 weeks. A total of 3 deaths occurred, none due to disease [25].

TFR Studies Involving Dasatinib

The DASFREE is a phase 2 study that enrolled patients who were on dasatinib for more than 2 years as first-line or subsequent therapy, with confirmed deep molecular response (MR4.5) for more than 1 year prior to enrolment, and achieved a 1-log reduction in *BCR-ABL1* from baseline within 3–6.5 months from the start of dasatinib. Relapse was considered as the loss of MR3. An interim analysis was presented with 71 patients enrolled out of 79 planned. The first 30 patients were presented and 11 patients lost MR3. EFS was 63% at 1 year. Median time on dasatinib prior to discontinuation was 40 months for patients who lost MMR and 55 months for patients who retained MMR. No transformation events or deaths were observed. After discontinuation, five patients had musculoskeletal adverse events [26].

The D-STOP trial is a prospective multicenter trial that discontinued dasatinib used as consolidation for 2 years in patients who had undetectable BCR-ABL1 levels after imatinib. Molecular relapse was defined as two successive positive RQ-PCR tests within 1 month.

Sixty-five patients received consolidation therapy and 54 discontinued dasatinib treatment after maintenance of deep molecular response for 2 years. The estimated overall TFS was 62.9% (48.5–74.2) at 12 months. There was no significant difference in estimated TFS between males and females or Sokal's score at diagnosis [27].

Second Discontinuation Attempt

The RE-STIM trial is a multicenter observational study that enrolled 70 patients who re-attempted a second discontinuation after the first failure. The loss of MR3 was the threshold to consider a patient in relapse. After a median follow-up of 38 months, 45 patients lost the response and the majority of relapses, as for the first discontinuation attempt, occurred within the first 6 months. The TFR at 12 months was 48% and at 36 months 35%. None of the patients progressed to a blast phase and the same TKI received before discontinuation was restarted in 27 relapsed patients (60%). At the last follow-up, 34 patients regained MR4.5 within a median time of 6.5 months. The analysis of prognostic factors associated to maintenance of molecular response after discontinuation showed that in patients who remained in deep molecular response within the first 3 months after the first discontinuation the TFR was 72% after the second attempt, whereas it was 36% for the others [28•].

The Japanese group reported on a second attempt of discontinuation in 10 patients treated with dasatinib who was restarted after failure of the first discontinuation: the drug-free survival was only 20% [29].

Prognostic Factors Associated to TFR

From all the studies discussed above, it emerged that the Sokal stratification, the duration of imatinib treatment and, for few studies, the previous exposure to interferon seem the best predictive factors associated with a positive outcome after discontinuation [9••, 11, 12•, 15, 17•]. The French group analyzed the immunologic compartment in 51 patients enrolled in the STIM1 study (IMMUNOSTIM) and found a low number of NK cells at the time of discontinuation in patients who subsequently relapsed [30]. The Nordic group analyzed the lymphocyte populations in 132 patients who were enrolled in the EURO-SKI study. Immunophenotype was performed at the time of discontinuation and then at 1.6 and 12 months after relapse. The results of the IMMUNOSTIM study were confirmed: patients who did not relapse after discontinuation showed an increased number of NK cells with cytotoxic phenotype (CD57+, CD56 dim) and an increased production of cytokines (IFNγ, TNFα) both at the time of discontinuation and at different subsequent time points. Molecular analysis was performed in NK cells that were found to be EAT2 down-regulated. The authors suggested an adaptive nature of these cells. No differences were detected between patients with or without previous exposure to IFN therapy. A trend was reported towards an increase of the NK cell population in low Sokal risk patients [31•]. Another subanalysis of EURO-SKI was also conducted to study the role of presenting antigen cells (pDC) that regulate lymphocyte T cell activation: 123 patients were investigated for the expression of CD86, a ligand of CTLA-4, an inhibitor of lymphocyte T cell activation. A cut-off of CD86+ pDC/10^5 lymphocytes > 95 was found to be an indicator of low relapse-free survival. Patients who relapsed had an increased number of CD8+PD1+ T lymphocytes (T cell exhaustion), without activity against residual disease [32]. The impact of polymorphisms of ABCG2, OCT1 and ABCB1 were also studied: no differences were observed in the expression of OCT1 and ABCB1 in relapsed and non-relapsed patients. Indeed, a weak difference was found in the expression of ABCG2 (1.1 vs 0.8%): patients with a higher value of ABCG2 normalized per GUS had a two-fold greater risk of relapse [33]. Finally, the UK group reported an increased risk of relapse for patients carrying an e13a2 type of transcript after discontinuation that needs to be confirmed in a large series of patients [34].

General Recommendations for Discontinuation

The last version of the 2013 European LeukemiaNet recommendations suggested to continue indefinitely TKI therapy and to appropriately discontinue only in a controlled clinical trial [35••]. Hughes and Ross reported for the first time in 2016 how to move TFR into the clinical practice, suggesting that patients who may be optimal discontinuation candidates should be non-high Sokal risk at diagnosis, with a typical transcript type, in CP with optimal past history of response with more than 8 years of treatment, in MR4.5 lasting for more than 2 years. Patients who should be excluded from a discontinuation proposal are patients with a prior advanced phase of the disease, in failure, with less than 3 years of treatment, not in MR4.5 and with a duration of deep molecular response of less than 1 year [36••]. A position on discontinuation was also taken by NCCN in the new version of the CML guidelines 2017: candidates to discontinuation are patients in chronic phase, on therapy with one of the available TKIs for more than 3 years, in stable MR4 for almost 2 years (documented on at least four tests performed at least 3 months apart) and no history of previous resistance. Monthly molecular monitoring for the first 6 months has been suggested in a standardized molecular laboratory with a limit of detection of MR4.5. The guidelines also suggested consulting with a CML specialty center to review the appropriateness for TKI discontinuation and potential risks and benefits. The threshold to consider for relapse is the loss of MR3 [37••]. Recently, ESMO guidelines indicates that optimal candidates to discontinuation are non-high Sokal risk patients, with typical quantifiable transcript, in chronic phase, after optimal response to therapy, who have reach MR4.5 with at least a stable MR4 for more than 2 years. Institutional requirements for safe supervision of TFR include availability of high quality internationally standardized, accurate and sensitive RQ-PCR laboratory, with rapid turn-around of test results (within 4 weeks) [38].

Patients' Perspectives about Discontinuation

Few studies have reported on the perception of patients regarding treatment discontinuation. We collected the results of a questionnaire administered to 1133 patients during regional meetings in Italy. We asked "*If in the future there is a perfect and long-lasting response to the treatment, would you accept the opportunity to interrupt the treatment for your illness?*"; 49% of patients answered that they would prefer not to interrupt treatment being afraid of losing the results achieved, while 16% of patients would like to discontinue due to long-term intolerance and 20% did not have a firm opinion [39]. A semi-structured interview to 40 CML patients showed perceptions about treatment discontinuation and TFR,

and on the potential impacts on QoL. Seventy-seven percent of patients had received information about TFR and 58% were cautiously positive about attempting discontinuation. The majority of patients interviewed would like to attempt discontinuation due to intolerance (75%) or for economic problems (58%). Ninety percent of patients expressed concerns about the possibility of developing resistance due to relapse or due to a low perceived likelihood of successfully maintaining a TFR [40]. Goldberg and colleagues also examined the perception about TFR in 210 patients invited by mail to answer a 27-item anonymous survey. The majority of them were on treatment for more than 5 years, and 19% were treated with a second-generation TKI. The survey specifically asked patients about propensity for discontinuation: 42% of them were willing to try, 34% wished to continue the TKI and 25% were uncertain. Most of the patients wanting to discontinue did so because of side effects (40%), economic problems (30%) and diminished inconveniences (26%). Most patients refusing discontinuation were worried about disease recurrence (58%) [41]. Finally, 87 patients answered a survey including CML-specific factors such as disease history treatment toxicity and adherence. The percentage of patients willing to discontinue increased to 81%; reluctance to attempt this strategy was associated with the need of additional information or a better understanding of the available data [42].

Conclusions

All the studies published so far clearly demonstrate that discontinuation is feasible and safe if performed in patients with a long-lasting deep molecular response, without reports of disease progression or clonal evolution. This possibility is changing profoundly physicians' behavior towards patients and TFR is always more frequently considered as a part of the routine clinical practice. The correct selection of the optimal candidates to discontinuation still remains a matter of debate and there is urgent need of general recommendations on how to identify patients and how to monitor them during the first months of discontinuation. Preliminary data on the use of second-generation TKIs does not seem to improve the results, but does appear to impact on the median time from treatment start to the stopping attempt. Patients' perceptions change over time and a better knowledge of the available data and specific communications will improve the attitude to participate to this strategy.

Compliance with Ethical Standards

Conflict of Interest Massimo Breccia has received compensation from Pfizer, Bristol-Myers Squibb, Incyte, and Novartis for service as a consultant.

Robin Foà has received compensation from Janssen, Gilead, Roche, Celgene, Amgen, AbbVie, Novartis, and Sandoz for service on advisory boards and/or speaker's bureaus.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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