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Cessation of Tyrosine Kinase Inhibitors in Patients with Chronic-phase Chronic Myelogenous Leukemia Following Durable Complete Molecular Response: A Single Center Facing the Dilemma

THEODOROS ILIAKIS[1], VASILIKI PAPADOPOULOU[1], PANAGIOTIS T. DIAMANTOPOULOS[1], PANAYIOTIS PANAYIOTIDIS[2], KONSTANTINOS ZERVAKIS[1], NEFELI GIANNAKOPOULOU[1], GERASSIMOS TILIMIDOS[1], MARIA ANGELOPOULOU[3], MARINA P. SIAKANTARIS[1], GERASSIMOS PANGALIS[4], MARINA MANTZOURANI[1], ELENI VARIAMI[1] and NORA ATHINA VINIOU[1]

[1]*Hematology Unit, First Department of Internal Medicine,*
[2]*Hematology Unit, First Propaedeutic Department of Internal Medicine and*
[3]*Hematology Clinic, Laiko Hospital, University of Athens, Athens, Greece;*
[4]*Hematology Clinic, Psychiko Medical Center, Athens, Greece*

Abstract. *Tyrosine kinase inhibitors (TKIs), namely imatinib mesylate (IM) and recently approved second-generation TKIs dasatinib and nilotinib, are currently considered the treatment of choice for newly-diagnosed chronic phase chronic myelogenous leukemia (CP-CML). Although treatment with TKIs has not yet been proven curative, it certainly accomplishes a sustained control of the disease in the vast majority of patients. More than a decade after the successful launching of IM in first-line treatment of CP-CML and the subsequent introduction of second-generation TKIs in this setting, the question of the possibility of TKI cessation in a specific subset of patients has emerged. Side-effects of TKIs, along with some patients' wish to abandon the drugs and the rising financial burden upon healthcare systems, have led to the dilemma whether IM can be safely withdrawn after achieving deep molecular remissions and which patients are suitable for this discontinuation. We examined the data of our patients with CML in search of potential canditates for cessation of TKI therapy and identified their characteristics. We also performed a thorough review of the relevant literature. Eight out of fifty patients were discriminated on grounds of sustained complete molecular response (CMR) exceeding 12 months, most of them with a low or intermediate Sokal score at diagnosis. The median interval from IM initiation to CMR was almost 2 years and the median duration of detected CMR reached 6.5 years. Based on the promising results of prospective clinical trials reporting successful cessation of treatment with TKIs on selected subgroups of patients, we decided to proceed to interruption of therapy in the specific subset of our patients and closely monitor their response.*

Correspondence to: Theodoros Iliakis, MD, Hematology Unit, First Department of Internal Medicine, Laiko Hospital, University of Athens, 17 Agiou Thoma Street, Athens 11527, Greece. Tel: +30 2107456207, Fax: +30 2107788830.

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Imatinib mesylate (IM) (Glivec®; Novartis), an oral inhibitor of the mutant Breakpoint cluster region-abelson (BCR-ABL) tyrosine kinase (TKI), represents the standard-of-care in the frontline treatment of chronic-phase chronic myelogenous leukemia (CP-CML) (1), making an innovative breakthrough in cancer treatment. The 8-year follow-up of the International Randomized Study of Interferon *vs*. STI571 (IRIS) study (2) demonstrated an overall survival rate of 85% for patients treated initially with IM and of 93% when considering CML-related deaths only. Subsequently, two even more potent oral BCR-ABL inhibitors, dasatinib (Sprycel®; Bristol Myers Squibb) and nilotinib (Tasigna®; Novartis), initially approved for patients with refractory disease or intolerance to IM, have also demonstrated excellent results in terms of cytogenetic and molecular responses as first-line therapy for CML and have gained relevant approval by the United States Food and Drug Administration (U.S. FDA), based on the results of the DASISION and ENESTnd studies, respectively. Recently published 3-year follow-up findings of both studies are very encouraging (3, 4) while longer follow-ups are eagerly awaited, enriching therapeutic options and establishing a debate on which of these available TKIs is the preferable initial choice in treating CP-CML.

Regarding the financial cost of these TKI-based approaches, in a recently published survey using data from the British National Healthcare System (5), first-line nilotinib appeared to be at least equally cost-effective to IM, which did not seem to be the case with dasatinib. However, the authors claim some uncertainty in the accuracy of the analysis and emphasize the need for additional data to support this conclusion. In addition, we should bear in mind that nilotinib and IM have similar prices in the United Kingdom, contrary to most European countries and the United States, where monthly nilotinib treatment is at least twice as expensive as the respective IM regimen.

During the past trimester, the U.S. F.D.A. approved two more compounds for the treatment of CP-CML and accelerated/blast phase CML (AP/BP-CML) cases not responding or intolerant to previous TKIs, namely bosutinib, an oral TKI (Bosulif®; Pfizer) and omacetaxine mepesuccinate (formerly homoharringtonine), an activation-induced cytidine deaminase inhibitor (Synribo®; Teva Pharmaceuticals). The former can be administered after at least one previous TKI drug failure regarding any CML phase (6), and the latter is administered subcutaneously to patients with disease resistant to at least two previous lines of TKI treatment (7), with the exception of BP-CML cases.

Both drugs gained approval after demonstrating significant improvement of cytogenetic responses in CP-CML and success in reinducing durable complete hematological responses in accelerated phases of the disease in a subpopulation of resistant and heavily pre-treated cases (6, 7). Notably, a significant subset of such patients had already received all three available oral TKIs. Unfortunately, the T315I *BCR-ABL* gatekeeper mutation, being insensitive to all currently used TKIs, confers resistance to bosutinib, as well. On the contrary, omacetaxine mepesuccinate has been active in a significant proportion of CML patients harbouring T315I mutant clones, holding promise for this group of patients with limited alternative options and persistently low response and survival rates (7). More recently, another oral TKI, ponatinib, has shown activity against resistant CML chronic or accelerated cases, including T315I mutant clones in a phase I trial (8).

Aim of the Study

We sought to distinguish the subgroup of our patients suffering from CP-CML, who might move on to cease their TKI treatment, on a firm ground of a sustained CMR. Data from the prospective CML8 and STIM studies (9, 10) supported such an attempt, provided that this approach develops under an extremely close monitoring of the patients' *BCR-ABL* transcripts, in the context of relevant clinical trials.

Patients and Methods

The sum of archived data of our living patients with CP-CML were examined, in order to identify canditates for TKI cessation. Candidates were defined as patients with CP-CML having received TKI therapy for at least three years and demonstrating sustained complete molecular response (CMR4) for at least 12 months, with at least three polymerase chain reaction (PCR) results with CMR4 within the last year before study entry and no results >0.01% during the same period. CMR4 was defined as either (i) detectable disease ≤0.01% *BCR-ABL* (IS), or (ii) undetectable disease in cDNA with ≥10,000 *ABL* transcripts. Patients on second-generation TKIs were included as candidates for TKI cessation, provided that they did not switch to a second or third drug on the grounds of first or second drug failure, but only on grounds of toxicity and, of course, provided they never lost their CMR4 status.

The quantification of *BCR-ABL* transcripts was performed at our Center's laboratory with reverse transcription of peripheral blood RNA and subsequent real-time PCR, using *ABL* as a reference gene and following a certified methodology, according to European standards (IPSOGEN *M-BCR-ABL* kit, compliant to the European Union *In Vitro* Diagnostics Directive and Biorad iQS instrument; all our patients were initially identified to have M-BCR-*ABL* transcripts).

Results

A total of eight patients who fulfilled the criteria for potentially discontinuing TKIs were identified out of our pool of patients with CP-CML. All eight patients currently receive IM, except one on nilotinib and all eight demonstrate durable CMR. All patients achieved CMR with undetectable *BCR-ABL* transcripts initially being on IM. The patients were diagnosed from May 1993 to February 2007. Their median age at diagnosis was 54.5 years (range=27-73 years) and the sex ratio was 0.6 M:F. Sokal score at diagnosis was low in four patients, intermediate in three patients, and high in one patient, while the relevant Hasford score ratio was 4:4:0. The median interval from IM initiation to CMR was 20.1 months (range=6-40 months). The median duration of detected CMR was 67.2 months (range=27-101 months) which corresponds to a median of 84.7 months (range=66-121 months) of total TKI treatment.

One of the patients had been diagnosed and treated in the pre-IM era, having mainly received interferon for almost six years. It should be noted that this patient abandoned this treatment for a whole two-year period, having a partial cytogenetic response, a status she maintained until this drug holiday came to an end and she agreed to start on IM. Another patient was submitted to co-treatment with anagrelide in the first two months of her IM course. The patient on nilotinib had already achieved CMR while on his initial IM treatment but had to switch to dasatinib and subsequently to nilotinib because of toxicity of the former compounds (facial swelling due to IM and pulmonary hypertension due to dasatinib), without losing CMR.

Table I. *Patient's characteristics*.

Patient no.	Age at diagnosis, years	Gender	Sokal/ Hasford score	Therapy previous to IM	Switching to other TKI on toxicity grounds	TKI treatment duration to reach undetectable BCR-ABL transcripts, months	Duration of continuous CMR under TKI treatment, months
1	57	F	L/I	IFN-α	–	8 (IM)	90 (IM)
2	63	F	I/I	HU+Anagrelide	–	12 (IM)	54 (IM)
3	61	F	H/I	–	–	20 (IM)	101 (IM)
4	47	F	L/L	–	–	6 (IM)	82 (IM)
5	73	M	I/L	–	–	33 (IM)	37 (IM)
6	68	M	I/I	–	–	40 (IM)	27 (IM)
7	40	F	L/L	–	–	18 (IM)	65 (IM)
8	27	M	L/L		DAS following IM, NIL following DAS	24 (IM)	Total of 82 (IM) 36 (DAS) 43 (NIL) 3

Pt indicates patient; CML, chronic myelogenous leukemia; IFN-α, recombinant interferon alpha; TKI, tyrosine kinase inhibitor; IM, imatinib mesylate; DAS, dasatinib; HU, hydroxyurea; CP, chronic-phase CML; L/I/H, low/ intermediate/ high Sokal or Hasford score; –, not applicable; NIL, nilotinib.

It is interesting to note that all patients currently receiving IM experienced fluctuations in their dosage due to various causes, such as intolerance or resistance to the compound, but at present, all of them follow the standard 400 mg daily schedule. The characteristics of the above mentioned patients are shown in Table I.

Discussion

Almost a decade after the introduction of imatinib in the treatment of CP-CML and with the addition of second-generation TKIs in this setting, greater expectations are justified. As previously mentioned, IM induces complete cytogenetic responses (CCR) in more than 85% of patients with CML and confers a significant survival benefit (2), while dasatinib and nilotinib achieve similar, if not superior, results, concerning all parameters, after 3-year follow-up as first-line CP-CML therapy (3, 4). The enthusiasm among hematologists, coupled with a substantial proportion of patients having difficulties in maintaining treatment adherence, even after reaching treatment targets, has turned the possible discontinuation of TKI treatment into a holy grail for the CML-treating community. In parallel, the economic burden of these effective but at present lifelong treatments upon healthcare systems should not be neglected.

Nevertheless, whether IM can lead to a cure remains controversial. The dilemma of whether to cease IM treatment arises from the conflicting results after such attempts, with certain patients retaining previously achieved molecular responses, while others experience relapse with recurrence of detectable *BCR-ABL* transcripts in peripheral blood (9, 10). At present, it is difficult to clarify in advance which patients or disease characteristics can safely guide us as to when to attempt to discontinue imatinib. However, there is a growing number of significant studies and case reports regarding patients with CML in whom otherwise successful treatment with IM was terminated for various reasons, with some of those experiencing molecular relapse but, fortunately, others not (9-20). Cessation of dasatinib or nilotinib with a successful outcome has also been reported (21, 22). In fact, the crucial question is the required depth of the molecular response and the necessary duration of IM treatment after achieving CMR before a safe discontinuation of the drug can be pursued. It is now widely recognized that some patients with CMR are able to sustain this response after discontinuation of IM. In the landmark prospective non-randomized multicenter STIM study, the Intergroupe Français des Leucémies Myéloïdes Chronique reported that among patients with a CMR maintained for at least two years (N=100), this response was sustained in 39% of patients 24 months after discontinuation of the drug (10, 23). This strategy undoubtedly requires further careful validation and much longer follow-up. However, it is remarkable that in this study, 56 out of 61 patients returned to CMR after rechallenge with IM; a median time of four months of treatment was necessary for restoration of CMR (23). Another study has also shown re-achievement of major molecular responses after resumption of IM in patients who experienced molecular relapse upon discontinuation (18). Notably, low Sokal score and longer previous TKI therapy were the only two independent factors predicting for non-relapse after IM cessation in the STIM study, while having been on previous treatment in the pre-IM era did not have an impact on maintaining nor on re-achieving CMR (10, 23).

The outcome of patients with CML in CCR after cessation of interferon-alpha (IFN-α) during the pre-IM era has also

been reported, and a proportion of patients, all of them notably showing negative real-time quantitative PCR did not experience relapse. On the contrary, in the case of residual disease with detectable *BCR-ABL* transcripts using PCR, patients in CCR experienced relapse after IFN-α interruption (24). Moreover, there has been a report of cessation of IFN-α in patients with CMR on this drug and outcomes were encouraging (25).

Several mechanisms of TKI failure and subsequent relapse have been proposed for patients with no apparent molecular evidence of the disease. The status of major molecular response is characterized by the persistence of CML clones with low *BCR-ABL* levels that may explain their insensitivity to IM and the propensity to exhibit resistance to the drug through point mutations in the tyrosine kinase domain (26). Additionally, the incurability of CML has, up to now, been attributed to both the existence of primitive, quiescent, Ph-positive stem cells insensitive to imatinib *in vitro* (27), and to residual *BCR-ABL*-positive hematopoietic progenitors present in patients who achieve a CCR/major molecular response with IM (28, 29, 30). Lastly, it has been postulated that CML stem cell survival might rather be *BCR-ABL* kinase-independent, suggesting the in efficacy of current solely TKI-based therapeutical approach (31).

Interestingly, among our patient group, those who demonstrated the more rapid CMR were the ones with a low Sokal score at diagnosis (median time=11 months), while, as expected, those with an intermediate/high score took longer (26.4 months) to reach this therapeutic milestone. Previous treatment with other agents (interferon/anagrelide), irrespectively of the scheme and the length of time administered, did not have an impact on achieving CMR, as also previously reported in the IRIS trial follow-ups (32-34), the main prognostic factor remaining the initial Sokal score. All our patients have already completed at least two years of durable CMR while on IM. Taking into careful consideration the constantly increasing encouraging data from various groups, we will be making the next step to move on without TKIs for these patients in the context of clinical trials.

In conclusion, despite promising results, the cure of CML has not yet been reached and life-long TKI therapy is still universally proposed (35, 36). Durable CMR is not infrequent and at our center it was identified at a percentage of about 16% of patients with CP-CML. Discontinuing IM in CML should only be considered in the context of carefully designed prospective multi-center clinical trials, with strict molecular monitoring. Only enrollment into such trials will provide us with the answer of whether a cure is feasible, indeed, in specific subsets of patients with CML and will assist us to clearly distinguish which individuals might benefit from this approach, without jeopardizing the excellent results of the current TKIs or depriving patients of the opportunity to cease treatment. Until the case is clear, the most prudent advice is not to try stopping IM at home (37).

Conflicts of Interest

No conflicts of interest to disclose.

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