

Future Perspectives of Tyrosine Kinase Inhibitors Discontinuation in Chronic Myeloid Leukemia

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Abstract

Stopping tyrosine kinase inhibitors (TKIs) treatment is an emerging goal of chronic myeloid leukemia (CML) management. Several studies have demonstrated the feasibility of stopping treatment. A sustained molecular response on long-term TKIs therapy seems to be necessary prior to attempting treatment-free remission (TFR). However, there were none available characteristics or indicators which can predict the outcome of TKIs discontinuation now. In our opinion, factors which could reflex the progression probability of minimal residual leukemia such as leukemia stem cells and microenvironment might play a pivotal role. Besides, novel methods for further monitoring would also attract much attention of the researchers in this area.

Keywords: Tyrosine kinase inhibitors discontinuation; Chronic myeloid leukemia; Leukemia stem cells; Microvesicles; Myeloid-derived suppressor cells

Introduction

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder characterized by the Philadelphia chromosome (Ph) resulting from a reciprocal translocation between chromosome 9 and 22, which encodes a constitutively active tyrosine kinase [1]. With selective BCR-ABL1 tyrosine kinase inhibitors (TKIs), increasing numbers of patients who remain on TKIs for years have undetectable minimal residual disease (UMRD), which could guarantee a long-term event free survival and almost entire life quality of healthy [2,3]. Most of the patients with UMRD have strong and urgent desire to discontinue TKIs due to the long-term costs and toxicity. A study of patients treated with several TKIs found that approximately one-third of patients experienced moderate to severe TKIs-related side effects [4]. Besides, patients who prepare for pregnancy also pay much attention to the cessation. Consequently, although life-long treatment is still recommended, treatment-free remission (TFR) is an emerging goal of CML management, which was already recommended by National Comprehensive Cancer Network (NCCN) guidelines [5]. In fact, several studies have demonstrated the feasibility of stopping TKIs and increasing studies will continue to validate the concept of TFR. The French CML Intergroup firstly reported TFR in the Stop Imatinib (STIM) study in less than 40% of 100 imatinib-treated patients who had maintained UMRD for >2 years [6]. The Australasian Leukaemia and Lymphoma Group Trial of Withdrawing Imatinib in Stable Remission (TWISTER) study reported almost identical results in 40 patients with similar clinical characteristics [7]. In our recent study, we performed a clinical observation of TKIs cessation including 22 Chinese CML patients. Approximately 55% of patients suffered molecular relapse and they remained sensitive to the same TKIs after molecular relapse [8]. This manuscript aims to provide an overview of current opinions and provide an outlook on future perspectives.

The first question of TFR achievement in concern is which part of patients would be eligible for discontinuation. Currently, most of the publications considered that a sustained deep molecular response on long-term TKI therapy seems to be necessary prior to attempting TFR achievement [9]. Molecular monitoring of BCR-ABL1 transcripts for patients with CML is now used to assess response to TKIs, including treatment failure that mandates an indicator of therapy. The level of BCR-ABL1 mRNA detected by standardized real-time PCR defined different level of response. MR4.5 (BCR-ABL1IS <0.032%) is available in some lab at present while other institutes remain MR4.0 (BCR-ABL1IS <0.01%). As mentioned above, patients in deep molecular response (at least MR4.0) have a rate of 40% TFR after stop TKIs [10]. However, patients who did not achieve molecular response would all relapse (100%) after cessation [10]. As a result, deep molecular response ought to be the access of discontinuation.

The next concern of TKIs cessation is about the relapse. In our recent study, we performed a clinical observation of TKIs cessation including 22 Chinese CML patients. At the end of follow-up, approximately 45% of patients recurred in detected BCR-ABL1 transcript levels [8]. In previous representative imatinib discontinuation trials, the French STIM study revealed that the relapse-free survival rate was 41% at 12 months after imatinib withdrawal, and a randomized HOVON study also showed a relapse rate of 67% [11]. In contrast to these studies, a lower rate of relapse could be seen in our study probably attributed to the short observation period, small number of patients observed or inclusion criteria. The standard of relapse mentioned above refers to patients lost their MR4.0. Recently, molecular relapse after cessation was expanded to a loss of major molecular response (MR3.0). As a result, the relapse rates relatively decreased: for instance 53% at 24 months in the Australian prospective TWISTER study and 33.7% in the multicentre prospective KIDS. The interim analysis of the STOP 2G-TKI study presented an opposite result in which 43.3% of patients experienced a molecular relapse defined as the loss of MMR at a minimum follow-up of 12 months [12].

One aspect that merits further consideration is what are the characters of patients who will suffer a molecular recurrence after discontinuation of TKIs? It was reported that there were several significantly independent factors predicting the risk of relapse, such as interferon-alpha prior to or in combination with TKIs, Sokal risk, types of transcripts of BCR-ABL1, time to MR3.0, count of natural kill cells, cytokines of NK cells and duration of stable UMRD before TKIs cessation [9]. Besides, the latest publications demonstrated that shorter treatment free survival was observed in patients with high frequencies CD56BRIGHT NK cells [13]. Besides, Timothy et al. have summarized some of the key factors that determine a patient's suitability for a TFR attempt [10]. But in my opinion, there were no available characteristics or indicators which can predict the outcome of TKIs discontinuation now, especially for one single person who would like to cessation, because these factors do not truly reflex the progression probability of minimal residual leukemia.

Minimal residual diseases in the CML patients are responsible for the post-cessation relapse. It is well known that although TKIs could effectively eradicate most CML cells, they are largely ineffective in depleting quiescent leukemia stem cells (LSCs) [14]. Chomel et al. demonstrated that CD34+ cells obtained from bone marrow of patients with sustained undetectable molecular residual disease for 3 years or more after TKI therapy were used in long-term culture-initiating cell assays, and BCR-ABL1-expressing LSCs were found in all [14]. We concerned that the minimal residual disease in patients refers to both the inherent properties of LSCs and the heterogeneity of microenvironment in bone marrow, which may play an important role in the determinant of relapse. Herrmann et al. demonstrated that CD45+CD34+CD38-CD26+ was the phenotype of CML-LSC and CD26+ were a new biomarker and the feature between normal stem cells and CML-LSC [15]. Our result showed that CD45+CD34+CD38-CD26+ cells could be detected in 20/22 patients even they have achieved UMRD for years, indicating that CML-LSC could not be eliminated by TKIs. However, no significant difference was observed in the number of CD45+CD34+CD38-CD26+ cells between the TFR group and the relapse group. Interestingly, lower number of CML-LSC in patients who have accepted 12 months or longer terms of IFN- α was observed. However, relapse could also be observed in the long-term IFN- α group, indicating it is some other character but not the number of CML-LSC was responsible for the relapse [8]. To identify the character of CML-LSC, we have performed single cell sequencing of LSC from the relapsers and non-relapsers by FACS sorting. Preliminary bioinformatics indicated that lipid metabolism showed significant difference between these two groups. In the future, more works ought to focus on the CML-LSCs in the cessation to tell the difference.

Leukemia associated microenvironment also contributes to the post-cessation relapse. Retrospective survey indicated that lower number of CD4+ T cells, natural killer cells and their derived cytokines were associated with lower chance of successful discontinuation [8-10]. However, the reason these immune compounds show difference in the patients who were about to withdrawal remained unknown. Myeloid-derived suppressor cells (MDSC) have been extensively studied in recent years owing to their role in suppressing immune responses of many pathological conditions, including cancer [16]. MDSCs could suppress T-cells and natural killer cells, as well as antigen-presenting cells, abrogating the beneficial immune response [17]. For MDSCs could be amplified by cancer cells, they might connect the CML-LSC and T cells. As a result, we assume that MDSC might play a pivotal role in the post-cessation relapse of CML patients. We discovered that total

number of MDSC in relapse group was significantly higher than those maintain a stable remission after cessation. Whether the patient would relapse seems to depend on the MDSC and ultimately on the ability of LSC. MDSC would provide a novel and useful model to analyze the function of LSC and predict the relapse, by establishing a kind of new risk stratification system.

On the other hand, available methods for deeper monitoring of the minimal residual disease are critical for treatment discontinuation trials and to identify molecular recurrence. Some novel methods such as next generation sequence, Nano-string and digital PCR will play a pivotal role. In addition to technological innovation, we purposed that switch of the target for monitoring, using standardized scheme, also becomes a new possibility. Our previous work demonstrated that CML cells derived micro vesicles (MV), small membrane-vesicles released by eukaryotic cells by outer cell membrane budding, contained mRNA of BCR-ABL1 [18,19]. Recognized as a package of extracellular multi-molecule messages, MV carries its parental cell proteins, lipids and nucleic acids, providing a potential source of disease-related biomarkers [20]. Our data demonstrated that detection of BCR-ABL1 mRNA by RT-PCR in MV could also define different response of CML patients, similar to the cellular BCR-ABL1 detection. More interestingly, BCR-ABL1 could be detected in MV even when the patient has achieved MR4.5. As known to all, MR4.5 could not guarantee the elimination of leukemia cells. That a few leukemia cells residual in the bone marrow and absent in peripheral blood would result in negative of RT-PCR. We could further speculate that the BCR-ABL1 positive MV detected when MR4.5 might probably be derived from CML-LSC. As one single cell could release large amount of MVs, the signal of LSC could be cascade amplified. Multiple studies have demonstrated that tumor cells themselves may locate in some undetectable sites, but secreted MVs are able to circulate in the blood, transporting information of the cancer [21]. As a result, MV would be useful for the CML-LSC monitoring and might sever as a novel factor for stratification of MR4.5. We discovered that P210 in MV of allo-PBSCT group was significantly lower than those taking TKIs although these patients all have achieved UMRD. It was believed that allo-PBSCT, rather than TKIs, was considered to cure CML. Difference of BCR-ABL1 in MV might provide novel insight of this conclusion. Besides, considering CML-LSC residual in the patients of MR4.5, the circulating BCR-ABL1-positive MVs were probably derived from these LSCs directly or indirectly. BCR-ABL1 in MV from the relapse group was higher than those in the TRF group and durative increased BCR-ABL1 in MV could be observed before the definitive proof of relapse, indicating that BCR-ABL1 copies in MV could be an early-warning indicator of relapse.

Conclusion

In conclusion, although discontinuation of TKIs has turn to the terminal goal of CML care and has caught increasingly attention, until safe criteria have been defined, drug cessation is still experimental and should be restricted to clinical trials or registries. The future in CML treatment will be to define criteria for the safe and most promising discontinuation of TKI on one hand, and, on the other, to increase the number of patients available for such an attempt. Novel routes of monitoring and elimination of LSCs are on urgent schedules. The idea of cessation will also provide an outlook on future challenges of leukemia stem cells and associated microenvironment.

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