



Tyrosine kinase Inhibitors in Chronic Myeloid Leukemia Patients in Complete Molecular Response: Continue or Discontinue?



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Abstract

Results of multiple prospective trials have demonstrated that patients who maintain deep molecular response for at least 2 years with TKI treatment may be eligible for TKI discontinuation. Approximately 40% of those who try to discontinue therapy will remain in remission at least 1 year after TKI discontinuation. This article try to illustrate the following: withdrawal syndrome after TKI discontinuation, factors which suggest successful treatment discontinuation, the patients who are not indicated for ABL TKI discontinuation, frequency of molecular monitoring after TKI discontinuation and future directions to increase proportion of patients with successful TKI discontinuation.

Abbreviations: TKI: tyrosine kinase inhibitors; NCCN: National Comprehensive Cancer Network; ELN: the European Leukemia Net; CML: chronic myeloid leukemia; QoL: quality of life; AEs: adverse events; MMR: major molecular response; IS: International Scale; MR4: molecular response 4; MR4.5: molecular response 4.5; UMRD: undetectable minimal residual disease; ENESTND: Evaluating Nilotinib Efficacy and Safety in Clinical Trials newly diagnosed; DASISION: Dasatinib Versus Imatinib Study in Treatment-Naive CML Patients; TFR: treatment-free remission; MRFS: Molecular recurrence free survival; IFN: interferon.

Introduction

The most recent recommendations of the NCCN and the ELN for CML propose indefinite continuation of TKI treatment in all responding patients. Survival rates of well responding patients to TKI therapy are similar to those observed in the general population, however expected and unexpected side-effects, impairment of QoL for many patients and financial burden must be considered [1]. TKI-associated AEs that affect daily living are observed in approximately 30% of patients, during long-term TKI therapy [2]. Their severity tended to remain relatively constant over time. This may be especially true for younger patients [3]. Imatinib treated patients showed impaired physical and mental health status in patients <60 years, whereas older CML patients on average had a health status comparable to age-matched controls [3].

Impairments in health-related QoL were also detected due to low-grade AEs in gastrointestinal disorders (e.g. diarrhea, nausea), blood disorders (e.g. thrombocytopenia, neutropenia), musculoskeletal disorders (e.g. muscle spasms, arthralgia), psychiatric disorders (e.g. anxiety, insomnia), and general disorders (e.g. fatigue, peripheral edema). Incidence rates of AEs in each category were similar or lower in patients receiving nilotinib 300 or 400mg twice daily versus patients receiving

Imatinib [4]. In addition, uncommon, potentially serious risks may emerge after months or years of long-term TKI treatment. Cardiopulmonary or atherosclerotic risks, may contribute to morbidity and even mortality with long-term use [4]. These risks include pleural effusion and pulmonary hypertension with dasatinib and vascular events with nilotinib. Imatinib appears to be relatively free of such late toxicities, but an accelerated decline in glomerular filtration rate has been reported. None of the TKIs are recommended for patients trying to conceive or during pregnancy or lactation [3].

Deep molecular response

Most patients on TKI therapy rapidly achieve CCyR and MMR (BCR-ABL1 \leq 0.1% on the IS). Many patients achieve MMR in the first 6 to 12 months of treatment. With continuing TKI treatment, many patients are able to achieve deep molecular responses, such as MR₄ (BCR-ABL1_{IS} \leq 0.01%), MR_{4.5} (BCR-ABL1_{IS} \leq 0.0032%), or UMRD; i.e. no detectable BCR-ABL1 transcripts [4]. MR_{4.5} occurs in ~20% of Imatinib-treated patients in the first 2 to 3 years, but this proportion rises to ~40% after 5 to 7 years. Using more potent TKIs, such as nilotinib and dasatinib, the rates of MR_{4.5} in the first 2 years are higher. As long as effective treatment is continued, the level of MRD may continue to fall

with very prolonged treatment. In the phase 3 ENESTND study, the rate of MR_{4.5} by 4 years was 40% with nilotinib 300 mg twice daily vs 23% with Imatinib 400 mg daily. In the DASISION study, MR_{4.5} was achieved by 3 years in 22% on dasatinib 100 mg daily vs 12% of patients on Imatinib 400 mg daily [3].

TKI Discontinuation

The results of multiple prospective trials have demonstrated that patients who maintain deep molecular response for at least 2 years with TKI treatment may be eligible for TKI discontinuation [5]. Recent reports suggest that approximately 40-60% of CML patients who have achieved deep molecular remission can discontinue Imatinib treatment [1]. Imatinib stop studies have been actively conducted around the world, including in Japan. In addition, several stop studies of second-generation ABL TKIs (dasatinib, nilotinib), which induce earlier response than Imatinib, have also been started [6]. At present, the TFR as a therapeutic goal has been gradually regarded as the new ultimate aim to patients with long-term CML [7] particularly those on second-generation TKIs [4]. However announcing a definitive cure remains a challenge owing to discovery that TKIs spare quiescent leukemic stem cells even in a patient in long-term TFR. For this reason a “functional” cure has been defined and proposed [8]. The mechanism by which patients maintain TFR despite low levels of residual disease is unknown but may involve immunologic control [4].

It was hypothesized that an increased amount of mature NK cells may be capable of both directly killing the tumor cells and potentiating adaptive immune responses against leukemia, thereby maintaining remission after Imatinib discontinuation [9].

A growing body of data suggests that some patients may be able to remain in TFR despite low levels of detectable BCR-ABL1 transcripts [1]. *BCR-ABL* mRNA level does not necessarily correspond to the number of residual CML cells [6]. Fluctuating BCR-ABL levels detected by qRT-PCR just below MMR without loss of MMR (and thus without re-treatment) is a common finding in A-STIM study. This suggests the importance of the role of immune surveillance for sustained TFR in CML [1]. Of patients in deep remission who stopped TKI therapy, 61% had no evidence of disease recurrence at 6 months and 52% had no evidence of disease at 18 months [10]. Mounting data indicates that approximately 40% of those who discontinue therapy on trial will remain in remission at least 1 year after TKI discontinuation [5] and even in defined deep molecular response throughout the duration of mostly 2 years follow up in other study [11].

Attempts at treatment discontinuation result in 60% relapses with molecular recurrence within the first 6 months in the majority of patients after TKI discontinuation [10]. Most relapsing patients regain the same depth of response after resumption of pre-discontinuation treatment [12]. The survival of patients who lost CMR following TKI discontinuation may not

be affected, even without re-administration of TKIs [13]. It has been reported that 20% of patients who made a second attempt achieved TFR [6] while there is small chance in other study on the second attempt of TKI discontinuation even with the use of second generation TKI [14].

Withdrawal Syndrome After Abl Tki Discontinuation

There are sporadic reports of approximately 15–30% of patients who suffered slight symptoms after discontinuation of Imatinib and other TKIs, such as muscle pain, joint pain, bone pain, rash, depression, weight loss, and others. The cause of withdrawal syndrome is still controversial. There are also psychological problems. A certain number of patients experience extreme fear of relapse caused by discontinuation of the drug. It has been reported that approximately half of patients are anxious that they will lose therapeutic response [6].

Musculoskeletal system adverse events are reversible on cessation of therapy. In the ongoing EURO-SKI trial, some patients reported musculoskeletal pain starting or worsening 1–6 weeks after STIM therapy. In a sub-cohort of the trial, it occurred in 15 out of 50 of patients. The pain was localized to various parts of the body, including the shoulder and hip regions and/or extremities, sometimes resembling polymyalgia rheumatica. Symptoms were mild in most individuals, leading to use of paracetamol or other non-steroidal anti-inflammatory drugs, but some were more severely afflicted with manifestations interfering with everyday activities and requiring steroid therapy. Over time these symptoms seem to resolve [1]. Only very minor laboratory abnormalities were noted in association with the musculoskeletal symptoms. Rate of molecular relapse in patients with musculoskeletal pain did not differ from those without these symptoms [1]. These findings support the concept of safe TKI treatment discontinuation and its usefulness for a specific subset of CML patients. However, recent data are not sufficient for TKI discontinuation attempts outside clinical trials yet [11].

Factors Which Allow Tki Treatment Discontinuation

If stopping CML treatment will be recommended in a well-defined patient population, the next step will be to think about how to increase patient numbers fulfilling these definitions. In this context, many factors have to be considered [1].

Basic Patient Characteristics And Line of Therapy

Line of therapy seems to play a role. So far, there is no indication that type or dose of TKI results in differences in discontinuation outcome [12]. A suboptimal response or resistance prior to dasatinib or nilotinib is associated with significantly worse treatment-free remission [15]. Longer duration of Imatinib therapy and duration of molecular response prior to TKI cessation were significantly associated with MMR status. Each additional 1 year of Imatinib treatment increased the odds to stay in MMR at 6 months by 16%. MRFS at 6 months

was 65% for patients who had been on Imatinib longer than 5.8 years compared with 42.6% for patients who were on Imatinib for 5.8 years or less [10]. Patients' risk profile at diagnosis [12], depth of molecular remission, and Sokal score, may be associated with a higher probability of attaining treatment free remission [5]. In the STIM study, male patients with low Sokal scores and a history of Imatinib administration of at least 50 weeks had a significantly low rate of molecular relapse after Imatinib discontinuation. In the TWISTER study and a retrospective study conducted in Japan, it was shown that a history of IFN- α use contributed to higher TRF rates [6].

Genetic And Immunological Parameters

The b2a2 transcript type has been consistently associated with lower response rates and longer times to response. An expression signature at diagnosis of 20 genes has recently been shown to correlate with outcome. Whether the early detection of low level resistance mutants with more sensitive detection methods, such as next generation sequencing provides an advantage for treatment choice and outcome remains a subject for discussion [12]. NK cell numbers were significantly different in early relapses (≤ 5 months after TKI stop) vs late relapses (45 months after TKI stop) denoting that different mechanisms may be involved in return of the disease at different time points. Whether NK-cell number and function may be used among other factors to predict disease relapse after TKI discontinuation needs to be further investigated. It further remains to be determined if pharmacological agent(s) that stimulate NK-cell function can increase the number of CML patients achieving deep molecular response and long-term TFR after TKI cessation [1]. Caocci et al reported that KIR polymorphisms could be significantly associated with better results of TFR. KIR2DL5B haplo types has already been reported to be significantly linked to the TKI response [16].

Leukemia stem cells (LSCs)

The detection of LSCs is not correlated with disease relapse. It has been shown that TKI may relocate quiescent CML stem cells to the endosteal niche making them difficult to be collected in bone marrow aspiration. Future studies of purifying putative LSCs in the marrow samples using recently described leukemic stem cell markers such as CD26 or IL1RAP are still needed. For a still unknown reason, leukemic colony-forming unit cells and long-term culture initiating cell isolated during TKI induced remissions express very low amounts of BCR-ABL1 mRNA [17].

The following patients are not indicated for ABL TKI discontinuation:

- (I) Those with intermediate or high Sokal scores;
- (II) Those tolerant of ABL TKI prior to treatment; and
- (III) Those with non-traditional *bcr-abl* transcriptional products (minor *bcr-abl*, etc.) that cannot be reliably monitored [6].

Frequency of Monitoring

The need for re-initiating therapy is necessary within 6-7 months in $\sim 45-60\%$ of patients. To avoid a fast and steep increase in BCR-ABL transcripts, frequent monitoring is strongly recommended. In most of the recent studies, this was done 4-weekly, after 6 months follow-up 6-weekly. If BCR-ABL transcripts are stable, thereafter, 3-monthly monitoring seems to be safe. This procedure has to be individually adopted according to the level of fluctuating transcripts [1]. However most TFR trials have continued monthly monitoring beyond this time. In the STIM1, A-STIM, and TWISTER TFR trials, patients who stopped Imatinib were monitored monthly for the first year, every 2 months for the second year, and every 3 months thereafter [4].

Future Direction To Increase Proportion Of Patients With Successful Tki Discontinuation

Many factors have to be considered, to improve the proportion of patients who stay free of relapse (i.e. no loss of MMR) for example, optimizing first-line therapy, and switching patients in MMR to other drugs to gain deeper MR. Further, the addition of other drugs, for example, IFN or stem cell active drugs, may also increase the proportion of candidates for cessation attempts [1].

LSCs exhibit aberrant or non-regulated self-renewal, survival and dormancy in comparison to normal stem cells. If molecular recurrence after stopping TKI is due to the persistence of LSCs, several strategies have been proposed to target LSCs including inhibiting survival/renewal pathways, sensitizing LSC (cycling or differentiating), immune targeting or modifying the bone marrow niche. JAK/STAT, JAK2 kinase, the protein phosphatase 2A, arachidonate 5-lipoxygenase gene, histone deacetylases, sirtuin 1 and BCL6 are among the most relevant targets for such a strategy [1]. Combined administration of Wnt/ β -catenin inhibitor, hedgehog inhibitor, etc to increase the TFR rate, both thought to be two of the most important pathways for self-renewal of CML LSCs [6]. A recent study demonstrated that it is possible to induce a kind of erosion of leukemic stem cells using a PPAR gamma agonist. Reduction of STAT5 activity cause gradual erosion of this cellular pool by regulating the pathway that controls quiescence in LSCs [1]. Testing of NK modulating agents is warranted for increasing the proportion of patients who can discontinue Imatinib treatment [9].

Conclusion

Many factors have to be considered in the future to improve the proportion of patients in deep molecular response who will stay free of relapse after TKI discontinuation.

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