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EDITORIAL

Evolving treatment strategies in CML – moving from early and deep molecular responses to TKI discontinuation and treatment-free remission: is there a need for longer-term trial outcomes?

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The management of chronic myeloid leukaemia (CML) evolved dramatically with the introduction of *BCR-ABL1* tyrosine kinase inhibitors (TKIs). Imatinib is the first TKI utilized in CML treatment, which was approved after the initial published data of the International Randomized Study of Interferon and STI571 (IRIS) trial, where **imatinib** was compared to combination of interferon alpha and low-dose cytarabine in patients with newly diagnosed chronic phase CML (CML-CP) [1]. Complete cytogenetic response and rate of progression to advanced disease was superior in the imatinib arm, and the responses to imatinib remained durable, as shown in the most recent update of the IRIS study with an estimated overall survival (OS) rate of 83.3% at 10 years within the imatinib group [2]. Nowadays, patients with CML-CP usually live near-normal life spans [3], and in a single-centre retrospective analysis, patients with CML-CP who were treated with TKIs in clinical trials had a 5-year OS estimated at 94.7% relative to the general population of the United States (US) within the era of TKIs [4].

During TKI treatment, response monitoring is essential, and molecular response (MR) is the most sensitive measure of response. MR classification is based on *BCR-ABL1* to control gene transcript ratios, expressed on the international reporting scale (IS), where major molecular response (MMR) or MR^3 is defined as $BCR\text{-}ABL1^{IS} \leq 0.1\%$, MR^4; $BCR\text{-}ABL1^{IS} \leq 0.01\%$, and $MR^{4.5}$; $BCR\text{-}ABL1^{IS} \leq 0.0032\%$. Early molecular response (EMR) is defined as $BCR\text{-}ABL1^{IS} \leq 10\%$ at 3 or 6 months of TKI treatment, and deep molecular response (DMR) is referred to MR^4 or $MR^{4.5}$ [5].

Nilotinib and **dasatinib** are second-generation TKIs (2G-TKIs), and they are more potent than imatinib with lower rates of transformation to advanced disease. These two TKIs were shown to be superior to imatinib including the speed and the depth of responses, and they are approved in the frontline treatment of patients with CML-CP in some countries following 2 phase III prospective, randomized, company-sponsored trials [6, 7]. Although more patients achieve EMR and DMR under 2G-TKIs than with imatinib, these drugs did not demonstrate a significant benefit in the long-term outcomes including progression-free survival and OS over imatinib, when used in the upfront setting in patients with CML-CP [8, 9].

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Bosutinib is another 2G-TKI, and this drug was proven to be efficient among imatinib resistant or intolerant cases. However, bosutinib 500 mg daily failed to demonstrate superior outcomes over imatinib in the BELA (Bosutinib Efficacy and Safety in Newly Diagnosed CML) trial, in which the primary endpoint was complete cytogenetic response (CCyR) at 12 months [10]. And consequently, bosutinib was not approved as a frontline treatment option for patients with CML-CP. BFORE (Bosutinib Trial in First-Line Chronic Myelogenous Leukemia Treatment) study, which is another multicentre phase III trial comparing frontline bosutinib 400 mg day with imatinib 400 mg daily was recently published [11]. Receiving a lower daily dose of bosutinib than that of BELA trial, patients on bosutinib had significantly higher rates of MMR and CCyR at 12 months and achieved responses faster than those on imatinib [11]. And the results of this trial led bosutinib to be approved as the fourth treatment option for newly diagnosed patients with CML-CP in the US.

In addition to these 2G-TKIs, **ponatinib** is a pan-*BCR-ABL1* inhibitor, which has potent activity against native and mutant *BCR-ABL1* including T315I. After the successful results in the salvage setting [12], ponatinib was tested as a frontline agent in newly diagnosed CML-CP patients [13]. In EPIC (Ponatinib in Newly Diagnosed Chronic Myeloid Leukemia) trial, patients were randomized to receive either ponatinib 45 mg daily or imatinib 400 mg daily; however, the study was terminated after a median follow-up of 5 months due to mainly arterial thrombotic events [13].

Treatment with TKIs should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs, and although generally well tolerated, 2G-TKIs have been associated with potentially serious (grades 3–4) adverse events (AEs) [14], which might result in permanent discontinuation of TKIs [15]. In addition to that, many patients experience low-grade (grades 1–2) AEs that might have a negative impact on quality of life [16], and adherence to novel oral therapies can be problematic in patients with cancer including cases with CML [17].

In patients receiving TKI therapy, drug–drug interactions should always be taken into consideration [18] and frequent monitoring for the detection of these potential interactions can be both inconvenient and challenging for the patients. So the possibility of safe TKI discontinuation may be beneficial among such patients, and sustained DMR may give patients an opportunity to temporarily discontinue TKI treatment (e.g. in female patients who want to get pregnant).

Furthermore, the economic impact of life-long TKI therapy is quite significant, and although the price of imatinib is expected to fall with the introduction of the generic formulations [19], long-term TKI therapy still puts a large financial burden to both patients and the health care systems [20].

Putting all these together, there are multiple potential motivators for achieving treatment-free remission (TFR) in CML patients with sustained DMR; however, in a recent survey, approximately 60% of the patients did not want to quit TKI therapy due to worries about disease recurrence, and the same analysis showed that the most common reasons for TKI discontinuation were AEs (40%), economic problems (30%), and reduction in inconvenience (26%) [21].

Other than CML, in which TKI therapy should be continued indefinitely in daily clinical practice, there are chronic conditions where patients need to receive long-term treatments. As TKIs can be discontinued in CML patients with sustained DMR in the context of clinical trials, antiepileptic drugs [22] or etanercept in rheumatoid arthritis [23] can also be discontinued safely at least in a subgroup of patients. When TFR is a treatment goal in CML, achievement of sustained (i.e. for ≥24 months) DMR is the key point. Since more patients achieve DMR with 2G-TKIs than with imatinib, choosing 2G-TKIs over imatinib may be beneficial in patients whom TFR is aimed. Results from the STop IMatinib 1 (STIM1) and TWISTER studies demonstrated that imatinib discontinuation may be feasible in CML patients who achieved sustained DMR. In STIM1, approximately 40% of patients maintained DMR at 1 year after discontinuing imatinib. These studies established achievement and maintenance of DMR as a prerequisite of successful discontinuation [24, 25]. Following these studies, many others were performed including patients receiving 2G-TKIs (nilotinib and dasatinib) both in the upfront and salvage settings [26]. And these studies showed that approximately 50% of the patients remained molecular relapse free. Thus, it is generally accepted that prior TKI therapy of 5 years and stable DMR ($\geq MR^4$) of 2 years or more constitutes reasonable minimal criteria for stopping TKIs.

If happens, molecular relapses typically occur within the first 6 months of discontinuation, and patients quickly regain their prior depth of MR upon rechallenging the same TKI [27]. In TFR trials, usually monthly real-time quantitative polymerase chain reaction monitoring for the first 6 to 12 months are required, with a gradual reduction in frequency thereafter [28]. Up to date, clinical progression of CML reported in a TFR study has been observed only once [29], although fear of progression could limit patient participation in trials as stated before.

Nonetheless, until the end of last year, TKI discontinuation was not recommended outside clinical trials, and on December 22, 2017, the Food and Drug Administration (FDA) approved the inclusion of TFR data in the nilotinib (Tasigna®) US product label [30, 31]. Adult patients with newly diagnosed CML-CP who were treated with nilotinib for ≥3 years and who have achieved DMR ($MR^{4.5}$) and CML-CP patients who received frontline imatinib and who has been switched to nilotinib due to resistance or intolerance and received nilotinib for ≥3 years and have achieved DMR ($MR^{4.5}$) may be eligible for treatment discontinuation.

This new approval was based on two single-arm trials, ENESTfreedom (NCT01784068) and ENESTop (NCT01698905) [32, 33]. ENESTfreedom were conducted in 190 newly diagnosed CML-CP patients who discontinued nilotinib after receiving it for ≥3 years [32]. Of the one-hundred and ninety patients, 51.6% and 48.9% remained in the TFR phase after 48 and 96 weeks, respectively. At the 96-week data cut-off, in cases with TKI rechallenge due to loss of MR, 98.9% and 92% regained MMR and $MR^{4.5}$, respectively [32]. In ENESTop, where one hundred and twenty-six patients who discontinued nilotinib after ≥3 years after switching from imatinib were recruited, 57.9% and 53.2% of the patients remained in the TFR phase after 48 and 96 weeks,

respectively [33]. At the 96-week data cut-off, among cases who restarted TKI treatment due to loss of MR, 92.9% regained DMR (MR^4 or $MR^{4.5}$). No patient in either trial progressed to advanced disease during TFR.

Currently, CML is a highly controllable disease in the era of TKIs, and TFR is a new therapeutic goal for the eligible patients. Although the data from the TFR trials suggest that a subset of patients with sustained DMR may safely discontinue TKI therapy and even after the recent FDA approval, as data from TFR studies continue to mature, the longer-term outcomes of these trials are still needed.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [34], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.

Competing Interests

A.E.E. has received honoraria for advisory board membership from Novartis and has received lecture fees from Novartis and Bristol-Myers Squibb. A.E.E. is a member of the *BJCP* Editorial board.

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