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EDITORIAL

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Tyrosine kinase inhibitor (TKI) therapy for newly-diagnosed patients with chronic myeloid leukemia: focusing on TKI discontinuation due to adverse events – is better always good?

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1. Introduction

The management of patients with chronic myeloid leukemia (CML) has changed dramatically with the introduction of imatinib. Although many patients with CML in chronic phase (CML-CP) achieve and maintain durable responses under imatinib, some need to be switched to alternative tyrosine kinase inhibitors (TKIs) due to intolerance and/or failure. After being first tested successfully in imatinib-resistant/-intolerant patients, second-generation TKIs (2GTKIs) (nilotinib, dasatinib, and bosutinib) were then utilized in the upfront setting and they were compared with imatinib among patients with CML-CP in three phase III prospective, randomized, company-sponsored trials [1–3]. Although bosutinib was proven to be efficient among imatinib-resistant or -intolerant cases, it failed to demonstrate superior outcomes over imatinib in the BELA (Bosutinib Efficacy and Safety in Newly Diagnosed CML) trial, in which the primary end point was complete cytogenetic response (CCyR) at 12 months [3]. Although the rate of major molecular response (MMR) in the bosutinib arm was significantly superior than that of patients receiving imatinib (41% vs. 27%, $p < 0.001$) as a secondary end point, the primary end point was not different for bosutinib (70%) versus imatinib (68%) ($p = 0.601$); consequently, bosutinib was not approved as a frontline treatment option for patients with CML-CP since the primary end point was not met [3]. Also in that study it was shown that the rate of discontinuation due to adverse events (AEs) was higher in patients receiving bosutinib 500 mg/day (19% – 48 patients) when compared to imatinib 400 mg daily (6% – 14 patients), and 15 (31%) of these 48 patients discontinued bosutinib before initial assessment, which might be one of the reasons for the low CCyR rates in the bosutinib arm. Gastrointestinal AEs were more common with bosutinib, such as diarrhea (70% vs. 26 %; $p < 0.001$), vomiting (33% vs. 16 %; $p < 0.001$), and alanine aminotransferase elevation (33% vs. 9 %; $p < 0.001$) [4]. In contrast, the hematologic and non-hematologic AEs that were less common with bosutinib were edema (peripheral, 5% vs. 12%; $p = 0.006$; periorbital, 2% vs. 14%; $p < 0.001$), musculoskeletal complaints (muscle cramps, 5% vs. 22%; $p < 0.001$; myalgia, 5% vs. 12%; $p = 0.010$; bone pain, 4% vs. 11%; $p = 0.003$), and neutropenia (13% vs. 30%; $p < 0.001$) [4]. The initial results of another multicenter phase III trial comparing frontline bosutinib 400 mg/day with imatinib 400 mg daily (ClinicalTrials.gov identifier: NCT02130557) were recently presented at an international meeting [5]. 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. In the near future, the results of this trial would most probably make bosutinib to be the fourth treatment option for newly diagnosed patients with CML-CP. However as in the BELA trial, more patients receiving bosutinib needed to stop TKI therapy because of toxicity than that of imatinib arm, and the percentage of patients who needed to discontinue the study drug due to drug-induced AEs in bosutinib and imatinib arms were 12.7% and 8.7%, respectively [5].

In addition to these treatment options, ponatinib is a pan-*BCR/ABL1* inhibitor, which potently inhibits all ABL mutations including T315I. After the successful results in the salvage setting, ponatinib was tested as a frontline agent in newly diagnosed CML-CP patients [6]. In EPIC (Ponatinib in Newly Diagnosed Chronic Myeloid Leukemia) trial, patients were randomized to receive 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 [6].

Knowing the fact that 2GTKIs are more potent than imatinib with lower rates of transformation to advanced disease (AD), these drugs are thought to be a better treatment option over imatinib in the upfront setting. Nilotinib and dasatinib were shown to be superior to imatinib regarding the speed and the depth of responses, but up to date, these drugs did not demonstrate a significant benefit in the long-term outcomes including progression-free and overall survivals (PFS and OS) over imatinib, when used as a frontline treatment option in patients with CML-CP. Although the rates may differ between different TKIs, all TKIs have hematologic AEs mainly appearing in the initial period of the tyrosine kinase inhibition. Some of the non-hematologic AEs are more related to a particular drug (e.g. dasatinib→pleural

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effusion (PE), nilotinib→peripheral arterial occlusive disease, etc.), whereas some appear as a class-effect. Also the potentially serious AEs of these newer TKIs might even be more hazardous than beneficial in a proportion of patients leading to both treatment interruption and/or discontinuation and these AEs might have negative impacts on adherence and health-related quality of life (HRQoL) [7].

2. Imatinib in the first-line treatment of CML-CP

In the 5-year follow-up data of the International Randomized Study of Interferon and STI571 (IRIS) trial, where first-line imatinib 400 mg/day was compared with interferon alfa plus cytarabine in patients with CML-CP, 382 patients out of 553 (69%) in the imatinib arm continued receiving TKI therapy, whereas 157 (28%) quit imatinib [8]. Among the patients who discontinued imatinib, toxicity-related treatment discontinuation was observed in only 23 (4%) cases. At 60 months, the rate of CCyR was 87%, and of these 382 patients who were still on imatinib at 60 months, 368 (96%) had a CCyR [8].

The 10-year update of IRIS trial demonstrating the long-term outcomes including OS, response to treatment, and serious AEs was recently published [9]. Among the patients in the imatinib group, the estimated OS rate at 10 years was 83.3%, and 267 patients (48.3%) who had been randomly assigned to imatinib completed study treatment with imatinib, and 82.8% had a CCyR. A total of 51 of 551 patients (9.3%) receiving first-line imatinib had a TKI-related serious AE, and the frequency of such events was highest during the first year of treatment and declined over time. No new safety issues were noted since the 5-year update [8], and 38 patients (6.9%) discontinued imatinib due to TKI-related toxicities in the final analysis [9].

3. Nilotinib in the first-line treatment of CML-CP

Two doses of nilotinib (300 or 400 mg twice daily) were compared with imatinib 400 mg daily among newly diagnosed patients with CML-CP in the ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinic Trials Newly Diagnosed Patients) trial [1]. MMR rates at 12 months and CCyR rates by 12 months were superior in both nilotinib arms than imatinib arm, and progression to AD was significantly lower in patients receiving nilotinib compared to those receiving imatinib. Progression to accelerated phase (AP) or blast crisis (BC) had occurred in 14 patients (11 patients (4%) receiving imatinib, 2 patients (<1%) receiving 300 mg of nilotinib, and 1 patient (<1%) receiving 400 mg of nilotinib) [1]. Both doses of nilotinib were also significantly better than imatinib with respect to the time to progression to the AP or BC ($p = 0.01$ for the 300-mg arm and $p = 0.004$ for the 400-mg arm) [1]. Also the rates of early and deep molecular responses (EMR and DMR) were higher with nilotinib than imatinib [1]. With this phase III prospective and randomized trial, nilotinib 300 mg b.i.d. was approved as an upfront treatment option for patients with CML-CP.

In the 5-year update of ENESTnd trial [10], more than half of all patients in each nilotinib arm (300 mg twice daily, 54%; 400 mg twice daily, 52%) achieved DMR compared with 31% of patients in the imatinib arm. The frequencies of AEs leading to discontinuation of study drug were comparable in the nilotinib 300-mg twice-daily ($n = 34$; 12.2%) and imatinib ($n = 39$; 13.9%) arms, and slightly higher in the nilotinib 400-mg twice-daily arm ($n = 55$; 19.9%) [10].

4. Dasatinib in the first-line treatment of CML-CP

In DASISION (Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients) trial, more than 500 newly diagnosed CML-CP patients were randomized to receive imatinib 400 mg or dasatinib 100 mg once daily [2]. CCyR rates at 12 months were significantly higher in the dasatinib arm than that in the imatinib arm, and then dasatinib 100 mg/day was approved in the frontline setting in patients with CML-CP. Progression to AD occurred in 5 of 259 patients who were on dasatinib (1.9%, all BC) and in 9 of 260 patients who were receiving imatinib (3.5%, all BC) [2].

In the 5-year update of DASISION trial [11], patients receiving upfront dasatinib 100 mg/day had better response rates with faster and deeper MRs than those receiving imatinib 400 mg/day. A higher percentage of dasatinib-treated patients achieved *BCR/ABL1* ≤ 10% [international scale (IS)] at 3 months compared with the imatinib arm (84% and 64%, respectively), and in both arms, patients who achieved *BCR/ABL1* ≤ 10% (IS) at 3 months more often reached CCyR, MMR, and $MR^{4.5}$ by 5 years [11]. However at the time of the analysis, there was no significant difference between the two study arms regarding PFS and OS. Focusing on the discontinuation rates of TKIs in this study, 42 patients (16%) discontinued dasatinib due to AEs, whereas intolerance was the reason for stopping the study drug in only 17 patients (7%) in the imatinib arm [11]. Particularly for TKI-related PE, this AE was more common with dasatinib (28%) than with imatinib (0.8%); however with proper supportive measures, only 15 patients (6%) required permanent discontinuation of dasatinib due to PE. The generation of PE did not impair the ability of patients to obtain a response [11], and these findings were consistent with the data that when dasatinib was used after imatinib failure, in patients who experienced grade I/II PE under dasatinib, continuing dasatinib together with management strategies induced durable responses [12]. In addition to that, the number of patients quitting the study drug due to failure were similar in both arms [28 (11%) and 36 (14%) for the dasatinib and imatinib arms, respectively], and at the time of the analysis, the number of patients on each study arms were comparable [162 (63%) vs. 158 (61%) for the imatinib and dasatinib arms, respectively] [11].

5. Newer TKIs versus imatinib in newly diagnosed patients with CML-CP

In a recently published systematic review and meta-analysis of eight randomized controlled trials comparing newer TKIs (nilotinib, dasatinib, bosutinib, ponatinib, and radotinib) with imatinib in terms of efficacy among patients with CML-CP in the upfront setting, the newer TKIs were found to be associated with greater MMR rates and lower rates of progression to AD but not with significant differences in CCyR, PFS, and OS [13]. Moreover, the percentage of patients who were still receiving the study drug at the 12-month follow-up point ranged from 68% to 87% for the

newer TKIs and 71% to 97% for the imatinib treatment groups. The main reasons for treatment discontinuation included AEs, disease progression, and treatment failure [13]. Knowing the fact that no significant difference between different TKIs is observed in terms of OS up-to-date, OS is obviously no longer the best end point for comparing the treatment outcomes, since the life expectancy of patients with CML approaches to that of general population in the era of TKIs [14].

6. Treatment-free remission (TFR) in patients with CML

Achieving and maintaining DMR may give patients an opportunity to temporarily discontinue the TKI treatment (for example in female patients who want to get pregnant), and TFR was investigated in several studies, first with imatinib and then with 2GTKIs (nilotinib or dasatinib) [15]. In these studies, patients experienced many potential positive impacts of TFR, and relief of TKI-related AEs were the most frequently reported, although discontinuation of TKIs could be associated with a toxicity, so-called 'withdrawal syndrome,' presenting with musculoskeletal pain which starts, or worsens after 1–6 weeks from TKI discontinuation [16]. In these trials, approximately 50–60% of the patients were molecular relapse free; however, the clinical data regarding the TKI discontinuation are still growing, and studies on large series should be planned in order to accumulate more mature data [17]. There are many factors that might have an influence on the decision of TKI discontinuation, and in a recent survey demonstrating the patients' perspective, approximately 60% of the patients did not want to quit TKI therapy due to worries about disease recurrence, and the most common reasons for TKI discontinuation included AEs (40%), economic problems (30%), and reduction in inconvenience (26%) [18].

7. Conclusions

The advent of TKIs has revolutionized the management of CML, and patients with CML-CP live near-normal life spans in the era of the TKIs. However, TKI therapy is not without toxicities, and even chronic low-grade AEs may interfere with the HRQoL of the patients. 2GTKIs (dasatinib and nilotinib) and imatinib can all be utilized in the first-line treatment of CML. Although these 2GTKIs are more potent and can induce faster and deeper responses than imatinib, they also have some serious non-hematologic AEs, which are not typically observed during imatinib treatment. So all factors including the characteristics of the patient (age, comorbidities, etc.) and the TKIs [19], together with the preferences of the patient should be considered prior to the initiation of TKI therapy in each individual patient together with the proper management of the AEs related to TKI exposure.

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Declaration of interest

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