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PROGRESS IN HEMATOLOGY

Chronic myeloid leukemia: the cutting-edge evidence and things we should know

Dose optimization of tyrosine kinase inhibitor therapy in chronic myeloid leukemia

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Abstract
The therapeutic outcomes of chronic myeloid leukemia (CML) have improved dramatically since tyrosine kinase inhibitors (TKIs) became available in clinical practice. Life expectancy of patients with CML is now close to that of the general population. Patients with CML who achieve sustained deep molecular response may discontinue TKI therapy. However, most patients still require TKI therapy for long periods without sustained deep molecular response. Given the awareness of increased incidence of arterial occlusive events in patients on TKI therapy, the optimal TKI selection should be based on age, comorbidities, risk classification, and goals of treatment. Dose optimization of TKI therapy reduces the incidence of adverse events while maintaining efficacy in CML.

Keywords CML · Tyrosine kinase inhibitor · Dose optimization

Introduction

Chronic myeloid leukemia (CML) is caused by the BCR::ABL1 fusion protein, resulting from the reciprocal translocation of the *ABL1* gene on chromosome 9 and the *BCR* gene on chromosome 22, which induces constitutive activation of the ABL1 kinase and confers tumor growth [1, 2]. Since the introduction of imatinib, a first-generation tyrosine kinase inhibitor (TKI) targeting BCR::ABL1, the 10-year overall survival (OS) rate in patients with CML has greatly improved to more than 80% [3]. Multiple randomized clinical trials and observational studies consistently showed second- and third-generation TKIs achieved faster and deeper response than imatinib [4]. Given the majority of the patients achieved response after TKI therapy, patients with CML in response can now expect normal life expectancy [5, 6]. Furthermore, patients in sustained deep molecular response are candidates for TKI discontinuation without TKI therapy [7, 8]. However, the fraction of patients in sustained deep molecular response is only 10–20% of patients with CML. Given the need of long durations of TKI therapy without sustained deep molecular response, the selection of optimal TKI therapy is required to minimize toxicity with the consideration of TKI-specific toxicity and patient's comorbidities [9, 10]. Second- and third-generation TKIs increased the risk of arterial occlusive disease (AOE) [11]. The consideration of patients' age, cardiovascular risk factors, and optimal dose of TKI therapy should be considered in CML [12–14]. In this review, we summarized the results of front-line TKI therapy with adverse events including AOEs, and recent studies on TKI dose modification.

Outcomes of front-line TKI therapy

The Japanese national insurance has approved imatinib, nilotinib, dasatinib, and bosutinib as first-line therapy in patients with CML. Ponatinib is approved for patients who are refractory to or intolerant of prior TKI therapy or who possess T315I mutation on ABL1 kinase domain. Recently, asciminib, a potent Specifically Targeting the ABL Myristoyl Pocket (STAMP) inhibitor, was approved for CML previously treated with two or more TKIs [15]. The selection

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of front-line TKI therapy should be based on comorbidities, financial status, known TKI-related toxicities, and risk classification, and goals of therapy in patients with CML. The European LeukemiaNet (ELN) 2020 panel [16] recommends periodic monitoring of molecular responses on the International Scale (IS) after initiation of first-line TKI and recommends a switch to alternative TKIs in case of treatment failure. All TKIs have shown excellent therapeutic efficacy against CML-CP. Prospective analysis of six consecutive or parallel prospective clinical TKI trials revealed that 5- and 10-year relative survival rates of patients with newly diagnosed CML-CP who achieved CCyR by TKI therapy were 97% and 92%, respectively [5].

Incidence of arterial occlusive events (AOEs)

The incidence of long-term adverse events has been investigated since the most of patients achieved response with stable disease course. The 10-year follow-up of the ENESTnd study also revealed a time- and dose-dependent increase in cardiovascular disease in patients on nilotinib compared to imatinib [17]. Among patients treated with nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, or imatinib 400 mg once daily, the incidence rates of cardiovascular events at 10 years were 16.5%, 23.5%, and 3.6%, respectively. The ENESTnd study showed worsening cholesterol and hemoglobin A1c levels in the nilotinib group compared to the imatinib group. Therefore, education for patients about cardiovascular risk and therapeutic intervention for dyslipidemia and diabetes are important to minimize the risk of cardiovascular events.

The 5-year follow-up of the DASISION study reported that ischemic heart disease occurred in 5% of the dasatinib group compared to 2% of the imatinib group [18]; peripheral arterial disease was observed in none of the dasatinib group and 1% of the imatinib group. Although the incidence of AOEs in the randomized clinical trials suggest higher incidence of AOEs in the second-generation TKIs, the difference in the eligibility criteria and unadjusted confounding factors did not allow the direct comparison between the second-generation TKIs. Similarly, Jain et al. analyzed 531 patients with CML-CP who were treated with TKIs as front-line therapy, and they reported that second-generation TKI therapy was associated with a higher risk of arterial thrombotic events compared with imatinib [11].

Bosutinib, a newer second-generation TKI, appears similar incidence of AOEs compared to imatinib in the BFORE randomized clinical trial [19]. Peripheral vascular events were observed in 4 cases in the bosutinib (1.5%) (1, angiopathy; 1, capillary fragility; 1, deep vein thrombosis; and 1, venous thrombosis in limbs) compared to 3 cases (1.1%) in the imatinib (2, peripheral coldness; 1, iliac artery occlusion); cardiovascular events occurred in 3.0% and 0.4% in the bosutinib and imatinib, respectively. The BELA study consistently showed relatively rare incidence of AOEs in patients during bosutinib therapy [20]. The incidence of cardiovascular events at 12 months was 0.8% in both bosutinib and imatinib arms.

Ponatinib, a third-generation TKI, is the most potent TKI available to inhibit wild-type BCR::ABL1 activity and maintains its efficacy for a wide range of ABL1 kinase domain mutations including T3151 mutation [21]. In the final 5-year results of the PACE study, the cumulative incidence of AOEs in 270 patients with CML-CP was 84 (31%), including 42 (16%) for cardiovascular events, 35 (13%) for cerebrovascular events, and 38 (14%) for peripheral vascular events [22]. Venous thrombotic events (6%) were also observed in the PACE study. Patients with cardiovascular risk factors or prior ischemic disease were reported to have a higher relative risk for AOEs.

The assessment by the Framingham risk score and the SCORE chart predicts for the incidence of cardiovascular events [23, 24]. The ELN group conducted a retrospective analysis using the SCORE chart and demonstrated its usefulness in patients on nilotinib [25]. For the risk management, the ABCDE steps have been proposed. The ABCDE represents acronyms of 3As (Awareness of cardiovascular disease; Aspirin; Ankle-brachial index), B (Blood pressure control), 2Cs (Cigarette cessation; Cholesterol), 2Ds (Diabetes; Diet), and E (Exercise). [26]. Given the older age of patients with CML, the implementation of the ABCDE steps is recommended at the initiation of TKI therapy.

Dose optimization of TKI therapy

Dose optimization minimizes the risks of adverse events while maintaining response to TKI therapy. Ponatinib-related AOE is dose-dependent and more frequently observed at a dose of 45 mg once daily. Dose reduction of ponatinib should be considered in patients with refractory CML in CCyR or deeper to minimize the risks of AOEs. A dose reduction of ponatinib by 15 mg/day reduced the risk of AOEs by 33% in a retrospective analysis of three clinical trials [27]. In the PACE study, the exposure-adjusted incidence of AOEs in patients with CML-CP was 15.8 and 4.9 per 100 patient-years in years 1 and 5, respectively. Because of the relatively high incidence of AOEs at year 1, a recommendation to reduce the dose of ponatinib from 45 to 15 mg/day in patients who had achieved MCyR was implemented during the PACE study. The dose reduction reduced the exposure-adjusted incidence of AOEs at year 5. Among patients who reduced the dose of ponatinib, more than 90% of patients maintained the response after the dose reduction [22]. The high response maintenance rates suggest dose

Table 1 Response of ponatinib and incidence of arterial occlusive events in the PACE and the OPTIC study

		PACE	OPTIC		
Ponatinib starting dose		45 mg	45 mg	30 mg	15 mg
≦1% BCR::ABL1 (IS) by 12 months (CCyR by 12 months)	Total	46%	51.6%	35.5%	25.3%
	T315I	66%	60.0%	25.0%	10.5%
Arterial occlusive events		31%	9.6%	5.3%	3.2%
Median follow-up (months)		56.8	32		

CCyR complete cytogenetic response, *IS* International Scale

reduction should be proactively considered in older patients and patients with multiple cardiovascular risk factors. Since the dose reduction was not a prospective intervention at a different level of response and timing in the PACE study, the optimal dose and timing of dose reduction of ponatinib were not clear from the PACE study.

The OPTIC (Optimizing Ponatinib Treatment in CML) trial was a randomized, open-label, phase 2 trial to explore a novel response-based dose reduction strategy for ponatinib [28] (Table 1). A total of 283 patients with refractory/resistant CML-CP (two or more prior TKI therapies or the presence of T315I mutation) were randomly assigned to ponatinib at 45 mg/day, 30 mg/day, or 15 mg/day. Patients in the higher dose groups were mandatory required to lower the daily ponatinib dose to 15 mg after the achievement of a BCR::ABL1 level of ≤ 1% on the IS. The primary endpoint was BCR::ABL1 level ≤ 1% on the IS at 12 months; its safety was assessed using rates of adverse events including AOEs.

The rates of BCR::ABL1 ≤ 1% at 12 months showed dose–response relationship; 44.1%, 29.0%, and 23.1% in the 45 mg/day, 30 mg/day and 15 mg/day, respectively. The cumulative incidences of BCR::ABL1 ≤ 1% by 12 months in patients with and without the T315I mutation were 60.0% and 48.5% in the 45 mg/day, respectively; 25.0% and 38.4% in the 30 mg/day, respectively; and 10.5% and 29.6% in the 15 mg/day, respectively. Compared to those without the T315I mutation, a lower proportion of patients with the T315I mutation achieved BCR::ABL1 ≤ 1% at the lower dosages, especially in the 15 mg/day. In the 45 mg/day and 30 mg/day, 73 patients (39%) reduced to 15 mg/day after the achievement of BCR::ABL1 ≤ 1%; among them, 55 patients (75%) maintained their response with a median follow-up of 32 months (range, 1–57).

The incidence of AOEs was dose-dependent in the OPTIC study. The incidence of AOEs was 9.6%, 5.3%, 3.2% in the 45 mg/day, 30 mg/day, and. 15 mg/day; the incidence of AOEs was lower than that reported in the PACE study given the dose optimization of ponatinib at earlier timing. Given a part of exclusion criteria is not the same between the PACE and the OPTIC study along with unadjusted confounders in the patient baseline characteristics, Kantarjian et al. reported the efficacy and safety of the OPTIC strategy with a propensity score analysis to adjust baseline confounders between the two studies. The PACE reported exposure-adjusted treatment-emergent AOEs of 9.3 incidents per 100 patient-years at 0 to 1 year while the OPTIC (45 mg → 15 mg) had exposure-adjusted treatment-emergent AOEs of 5.6 occurrences per 100 patient-years at 0 to 1 year. After adjusting baseline covariates, the OPTIC strategy achieved a 64% reduction in AOEs incidence compared to the PACE among all patients [29]. Benefit/risk assessment in the OPTIC study showed a starting dose at 45 mg/day to be associated with a 6.4% increase in AOEs but also a 26.3% increase in response rate compared to the 15 mg/day [28] (Table 2). Given the increment of response rates was higher than the increment of AOEs, the consideration of the risk/benefits for ponatinib therapy is essential to treat patients with refractory CML, particularly in patients with T315I mutation [30] (Table 3).

Dasatinib dose optimization has also been analyzed in a retrospective and prospective manner. Retrospective analysis of the DASISION trial showed that 37% of patients treated with dasatinib were required to decrease their treatment dose to 83 mg/day among patients on dasatinib at the end of the follow-up [31]. The most common reason for dose reduction of dasatinib was pleural effusion (30 patients; 12%). The reduced dose of dasatinib maintained a molecular response.

Naqvi et al. reported a long-term follow-up analysis of a prospective study to examine the efficacy and safety of low-dose dasatinib (50 mg/day) as front-line therapy in 81 patients with newly diagnosed CML-CP [32]. The cumulative achievement of CCyR, MMR, MR4.0, and MR4.5 by 12 months was 95%, 81%, 55%, and 49%, respectively. Five patients (6%) developed pleural effusion, and four of them required dose reduction of dasatinib. In the DASISION study, the cumulative achievement of 12-month MMR and MR4.5 was 46% and 5%, respectively; the efficacy of low-dose dasatinib (50 mg/day) in this study was better than that of dasatinib at 100 mg/day in the DASISION study and other pivotal prospective trials. The authors speculate that the improvement may be due to the less toxicity and better adherence to therapy without toxicities and interruptions.

Table 2 Risk/benefit analysis in the OPTIC study

Ponatinib dose	45 mg → 15 mg	30 mg → 15 mg
Improvement in achievement of ≦1% BCR::ABL1 (IS) by 12 months	Δ26.3%	Δ10.2%
Increase in occurrence of TE-AOE	Δ6.4%	Δ2.1%

TE-AOE treatment-emergent arterial occlusive event, *IS* International Scale

Table 3 Reported response by each cohort and mutation status in the OPTIC study

Ponatinib dose	45 mg → 15 mg		30 mg → 15 mg		15 mg	
Mutation status	No T315I	T315I	No T315I	T315I	No T315I	T315I
	N = 66	*N* = 25	*N* = 73	*N* = 23	*N* = 71	*N* = 19
≦1% BCR::ABL1 (IS) by 3 years, *N* (%)	36 (54.5%)	15 (60.6%)	30 (41.1%)	5 (25.0%)	31 (43.7%)	2 (10.5%)
3-year outcomes, %						
Progression-free survival	71	75	75	49	74	61
Overall survival	90	86	93	79	94	85

Table 4 Reported response of dasatinib by administered dose

Starting dose of dasatinib	100 mg/day (DASISION)	50 mg/day (Naqvi et al.)	20 mg/day (Murai et al.)
MMR by 12 months	46%	80%	60%
MR4.5 by 12 months	5.0%	49%	13.5%

MMR major molecular response, *MR* molecular response

The strategy of dose optimization may lead to the improvement of deep molecular response.

More recently, Murai et al. reported the results of the DAVLEC study, in which 52 patients with newly diagnosed CML-CP older than 70 years were treated with dasatinib at a starting dose of 20 mg/day [33] (Table 4). The primary endpoint was the achievement of MMR by 12 months of therapy. The response to dasatinib 20 mg/day was assessed every 3 months on the IS. The median age of patients was 77.5 years (range, 73.5–83.0). The 12-month MMR rate was 60%; at 3 months, 39 (75%) and 11 (21%) achieved BCR::ABL1 ≤ 10% (IS) and > 10% (IS), respectively (2, unavailable). Four patients (8%) had pleural effusions (only grade 1–2); no pulmonary hypertension was observed. Five patients ($n = 3$, hematological; $n = 2$, non-hematological) required median dose interruptions of 7 days. The response-based dasatinib therapy starting at 20 mg/day was shown to be effective and safe in elderly patients with comorbidities. AOEs were not reported in the DAVLEC study with a median follow-up of 366 days.

The ENESTnd study reported nilotinib 400 mg twice daily was associated with the development of AOEs more frequently than nilotinib at 300 mg twice daily; the incidence of cardiovascular events at 10 years was 23.5% and 16.5% in nilotinib 400 mg twice daily and nilotinib 300 mg twice daily, respectively [17]. The ENESTxtnd study evaluated the response-based dose optimization of nilotinib in patients with newly diagnosed CML-CP who started nilotinib at 300 mg twice daily. Among 421 patients in the ENETxtnd study, the cumulative 12-month and 24-month MMR rates were 70.8% and 81.0%. Among 88 patients (20.9%) who required dose escalation to 400 mg twice daily due to suboptimal response, 56 patients (63.6%) achieved MMR by 24 months of therapy; among 74 patients (17.6%) who required dose reduction due to toxicities, 55 patients (74.3%) achieved 24-month MMR by 24 months. The overall incidence of cardiovascular events was 4.5% [34]. The GIMEMA group reported the results of the ENEST1st study which reported similar efficacy and safety for the treatment with nilotinib at 300 mg twice daily. The achievement rate of MMR at 12 months was 56.3% [35]. In the ENESTxtnd study, 162 patients (38.4%) required dose optimization of nilotinib. The median actual daily dose intensity was 599 mg/day. Nilotinib at 300 mg twice daily was determined to be the standard of care.

The standard dose of bosutinib is 400 mg/day in patients with newly diagnosed CML-CP based on the results of two randomized clinical trials, the BELA (bosutinib 500 mg/day) and the BFORE (bosutinib 400 mg/day), compared to the standard dose of imatinib 400 mg once daily. The discontinuation rate of bosutinib was reported 29% and 22% in the BELA study and the BFORE study, respectively [19]. The starting lower dose of bosutinib may identify tolerable dose in older patients. In the BEST trial, elderly (> 60 years old) patients with resistant/intolerant CML were treated with bosutinib at a starting dose of 200 mg once daily [36]. 71% of patients continued their treatment with a dose of 300 mg or less, and 60% of patients achieved MMR by 12 months. A lower starting dose of bosutinib at 300 mg once daily may be more tolerable while maintaining efficacy in older patients.

As for imatinib, there are several reports that suggest lower dose of imatinib at diagnosis for older patients with CML-CP based on comorbidities and physicians' judgment [37, 38]. Given the high-risk features and the experiences of progression to blast phase shortly after imatinib therapy, the reduced dose of imatinib requires close monitoring to prevent the progression though lower dose of imatinib is more tolerable with less interruptions.

Future perspectives

Dose optimization of TKI therapy has been proposed to reduce their toxicity for its long-term use. Based on the patient's comorbidities, medical history, lifestyle, CML risk

classification, and the presence of mutations in the ABL1 kinase domain, a therapeutic goal must be individualized given the suboptimal outcomes at the time of progression [39–45]. Close monitoring for response and adverse events optimizes the management of patients with CML along with supportive therapy [46–49]. The treatment goal of CML may range from treatment-free response to maintain CCyR or deeper for long-term TKI therapy. Dose optimization will minimize the risk of cardiovascular events. Novel prognostic model may guide the selection of TKI therapy with consideration of patient background and pre-existing conditions [50]. In summary, TKI therapy for CML can be tailored by the optimal selection and dosage of TKI for each patient to achieve individual therapeutic goals. When patients are under treatment-free response, periodic monitoring is required to prevent the progression [51].

Declarations

Conflict of interest YU declares no conflict of interest. KS received honoraria from Otsuka and research funding from Novartis and served on advisory boards of Pfizer Japan, Novartis, and Takeda.

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