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REVIEW

Dose Optimization of Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia

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Abstract: With the advent of newer treatments such as new molecular targeted agents and immunotherapies, the model that selects therapeutic doses on the basis of the maximum tolerated dose is no longer relevant. The emergence of tyrosine kinase inhibitor (TKI) therapy has changed the treatment prospects for chronic myeloid leukemia (CML) and prolonged the long-term survival of CML patients. However, long-term exposure to TKIs is accompanied by adverse events, which may lead to disease progression and even death. It can also increase economic pressure on patients and affect their health-related quality of life. In general, dose reduction is feasible and safe for most patients and can reduce the incidence of adverse events while ensuring efficacy, reduce the financial burden on patients and society, improve the quality of life of patients, and also as a prelude to an attempt at treatment-free remission (TFR). This review will classify the dose optimization of all approved TKIs (imatinib, dasatinib, nilotinib, bosutinib, ponatinib, asciminib, radotinib) at different stages of treatment based on clinical trials and real-life studies, including dose optimization prior to attempting TFR. In addition, we briefly describe the application of therapeutic drug monitoring in dose optimization and the potential benefits of dose optimization on health-related quality of life.

Keywords: tyrosine kinase inhibitor, dose optimization, chronic myeloid leukemia, therapeutic drug monitoring

Introduction

For over 70 years, cytotoxic drug development in oncology has emphasized that higher doses yield greater antitumor effects. With the advent of newer treatments like new molecular targeted agents (MTAs) and immunotherapies, the model that selects therapeutic doses on the basis of the maximum tolerated dose (MTD) is no longer relevant.[1–3] Compared to traditional chemotherapy agents, MTAs and immunotherapies exhibit novel mechanisms of action, enhanced efficacy, and distinct safety profiles. Their target saturation limits are often below the MTD, indicating that administration at lower doses can achieve comparable efficacy while minimizing adverse effects.[1–3]

Chronic myeloid leukemia (CML) is a malignancy affecting the blood and bone marrow and is defined by the presence of the Philadelphia chromosome as a result of a reciprocal translocation between chromosomes 9 and 22 [t9;22], resulting in the BCR::ABL1 fusion gene.[4] Tyrosine kinase inhibitor (TKI) therapy is a highly effective treatment option for patients with chronic phase–CML (CP-CML). The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CML (version 2.2024) recommended imatinib and second generation (2G) TKIs (dasatinib, nilotinib, or bosutinib) as first-line therapy. Besides, ponatinib and asciminib (specifically targeting the ABL myristoyl pocket inhibitor) are active against most of the resistant BCR::ABL1 kinase domain mutants including T315I,[4] and Radotinib has so far received marketing authorization exclusively in South Korea.[5]

However, long-term exposure to TKIs is accompanied by adverse events (AEs) that may lead to disease progression and even death.[6,7] Especially 2G TKIs may increase cardiovascular risks, such as arterial ischemic events (coronary heart disease, stroke) and pulmonary hypertension.[8–10] A prediction model for the failure of TKI treatment was found that 20–30% of patients failed the treatment due to drug resistance or toxicity. Among them, the cumulative failure rate of the

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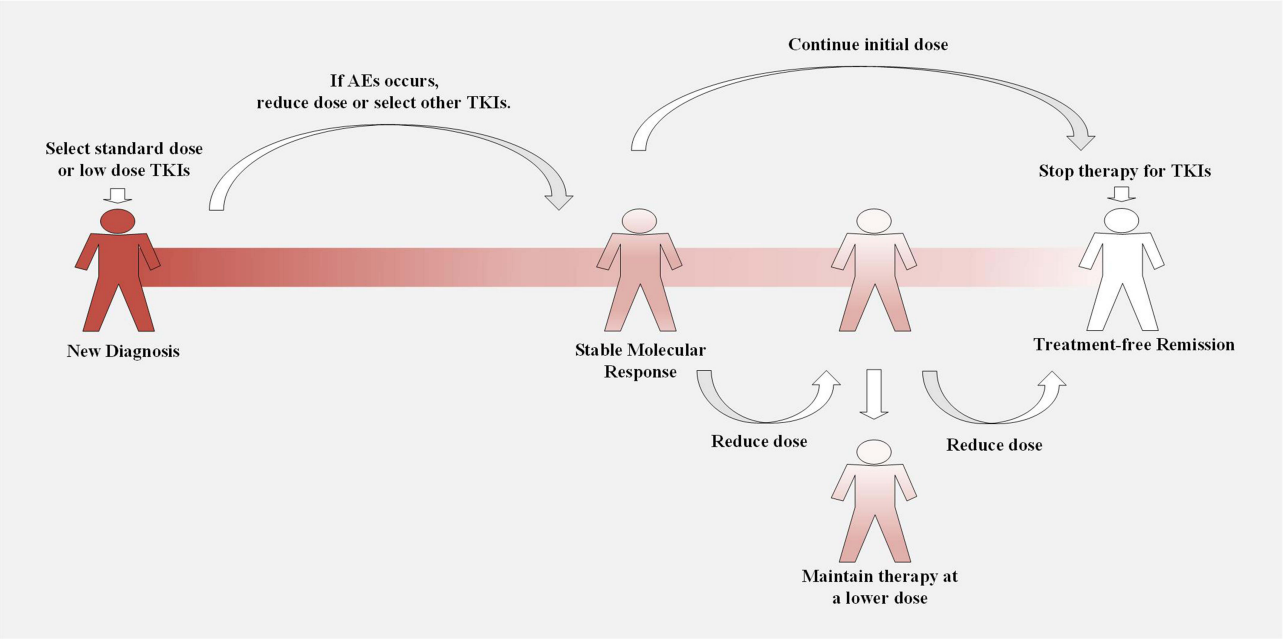

Figure 1 Dose optimization in the course of disease treatment.

high-risk group in 8 years reached 69%, and it was significantly correlated with the risk of disease progression.[11] After long-term TKI treatment in elderly patients (>75 years old), the proportion of non-CML-related deaths (such as infections and cardiovascular events) was as high as 40%, suggesting that age and the cumulative effect of toxicity synergically increase the risk of death.[12] Long-term exposure to TKIs can also increase economic pressure on patients and affect their health-related quality of life (HRQOL). Many AEs occur early in treatment and are dose-dependent, and thus they can be managed by dose modifications.[13] Optimally responsive patients may be overtreated with standard doses of TKIs. In addition, TKI significantly improved the outcomes of patients with CML. Treatment-free remission (TFR) is now the new goal of CML therapy. Prior to achieving TFR, dose optimization is implemented to balance efficacy and safety, thereby creating conditions for subsequent treatment discontinuation.

In this review, we classified the dose optimization of all approved TKIs (imatinib, dasatinib, nilotinib, bosutinib, ponatinib, asciminib, radotinib) at different stages of treatment according to the results of clinical trials and real-life studies, including pre-TFR dose optimization (Figure 1). We also discussed TKI dose optimization on the basis of therapeutic drug monitoring (TDM) and the HRQOL of patients after dose optimization, aiming to offer critical references for individualized clinical treatment for patients with CML.

Dose Optimization of Imatinib

Imatinib (Glivec; Novartis), the first TKI, was approved in 2001 in the United States and Europe for the treatment of all CML stages. Although the standard dose of 400 mg is usually well tolerated by most patients, studies have shown that AEs and overtreatment still exist. There have been several studies on post-marketing dose optimization of imatinib, including in elderly individuals (Table 1).

Dose Optimization in Patients with Newly Diagnosed CP-CML

After a large number of clinical trials and studies, 400mg daily was finally determined as the initial dose of adult CML in the chronic phase rather than 800mg daily, although 800mg daily induced a quicker and deeper molecular response.[14–20] There are limited data regarding starting imatinib at doses less than 400 mg daily, with the exception of elderly patients with serious comorbidities and polypharmacy. However, the results revealed that imatinib plays an important role in first-line treatment of

Table 1 Studies of Imatinib Dose Optimization

Study	Publication Time	Country	Types of Design	Patients	Intervention	Efficacy Endpoints	Outcome
Deininger et al[14]	2014	USA, Canada	Clinical trial (NCT00070499)	153	400 mg vs 800 mg	MMR CCyR	The MMR rates were 53% in IM800 and 36% in IM400 at 12 months (P=0.065). The CCyR rates were 85% in IM800 and 67% in IM400 at 12 months (P=0.040).
Cortes et al[15]	2009	USA	Clinical trial (NCT00081926)	115	800 mg	MMR CCyR	MMR rate was 54% and CCyR rate was 85% at 12 months.
Cortes et al[16]	2010	USA, Australia, Italy, et al	Clinical trial (NCT00124748)	476	400 mg vs 800 mg	MMR CCyR	The MMR rates were 46% in IM800 and 40% in IM400 at 12 months (P=0.2035). The CCyR rates were 70% in IM800 and 66% in IM400 at 12 months (P=0.3470).
Hughes et al[17]	2003	USA, Australia, Switzerland et al	Clinical trial (NCT00333840)	1106	400 mg IM vs interferon plus cytarabine	MMR CCyR	The MMR rate was 39% and CCyR rate was 68% at 12 months in IM400 arm. The MMR rate was 2% and CCyR rate was 7% at 12 months in interferon plus cytarabine arm.
Hehlmann et al[18,19]	2014	Germany, Switzerland	Clinical trial (NCT00055874)	820	400 mg vs 800 mg	OS PFS	10-year OS were 80% with IM400 and 79% with IM800. 10-year PFS were 80% with IM400 and 77% with IM800.
Baccarani et al[20]	2009	Italy	Clinical trial (NCT00514488)	216	400 mg vs 800 mg	MMR CCyR	The MMR rates were 40% in IM800 and 33% in IM400 at 12 months. The CCyR rates were 64% in IM800 and 58% in IM400 at 12 months (P=0.435).
Crugnola et al[21]	2019	Italy	Retrospective study	263	400 mg vs 300 mg vs <300 mg	MMR CCyR	Cumulative rates of CCyR and MMR were 69.9% and 56.2% respectively.
Latagliata et al[22]	2013	Italy	Retrospective study	211	400 mg vs.>400 mg vs <400 mg	MMR CCyR	The MMR rates were 52.1% with IM400 mg and 32.8% with IM below 400 mg at 12 months (P=0.040). The CCyR rates were 68.9% with IM400 mg and 51.1% with IM below 400 mg at 12 months (P=0.015).
Carella et al[23]	2007	Italy	Case report	4	400 mg to 200 mg	RQ-PCR	The median duration of RQ-PCR negativity on IM 200 mg daily was 17 months (4–37).
Park et al[24]	2007	Korea	Retrospective study	9	400 mg to 300 mg or 200 mg	CCyR	The CCyR rate was 77.8% during a median follow-up of 19 months. The toxicity was reduced from grade 3 or 4 to grade 2 or 1.
Cervantes et al[25]	2017	Spain	Retrospective study	43	400 mg to 300 mg	Loss of MMR	At the last follow-up, only one patient had lost the DMR and none lost MMR.
Clark et al[26,27]	2017	UK	Clinical trial (NCT01804985)	IM:148 DAS:10 NL:16	Half-dose before discontinuation	Loss of MMR	7% of patients had molecular recurrence during the 12 months of half-dose therapy. After a further 24 months of monitoring in TFR, the recurrence-free survival rate was 72% in the DMR group and 36% in the MMR group.
Luo et al[28]	2022	China	Clinical trial (NCT04143087)	IM:100 DAS:11 NL:14	Half-dose vs Discontinuation	Loss of MMR	The molecular recurrence-free survival rates were 88.32% in the de-escalation group and 59.98% in the discontinuation group at 12 months.
Russo et al[29]	2013	Italy	Clinical trial (NCT00858806)	76	Intermittent treatment	Loss of MMR	With a minimum follow-up of 4 years, 17% of patients lost CCyR and MMR and 18% of patients lost MMR only.
Malagola et al[30,31]	2021	Italy	Clinical trial (NCT02326311)	IM:140 DAS:20 NL:25	"Fixed" intermittent vs "Progressive" intermittent	Loss of MMR	The 1-year probability of maintaining the MMR was 81%. The 3-year probability of maintaining the MMR was the FIXED vs PROGRESSIVE arm (59% vs 53%, respectively P=0.13).
Saussele et al[32]	2018	France, Germany, Sweden et al	Clinical trial (NCT01596114)	IM:710 DAS:14 NL:33	Discontinuation	Loss of MMR	Molecular relapse-free survival rates were 61% at 6 months and 50% at 24 months.
Cayssials et al[33]	2020	France	Retrospective study	IM:49 DAS:21 NL:6	Full-dose before discontinuation vs Low-dose before discontinuation	TFR	TFR at 12 months was 56.8% in the full-dose TKI group and 80.8% in the low-dose group, and TFR at 60 months was 47.5% and 58.8%, respectively.
Verma et al[34]	2022	India	Retrospective study	IM:19 DAS:2 NL:8	400 mg reduced by 25% every 6 months	TFR	52.9% of patients have successfully stopped TKI for median duration of 11 months.
Rousselot et al[35]	2015	France	Clinical trial (EudraCT number 2008–006854-17)	133	TDM	MMR	At 12 months, 63% of patients achieved MMR after dose adjustment in A1 and 37% of patients achieved MMR with standard management in A2 (p=0.031).

Abbreviations: IM, imatinib; DAS, dasatinib; NL, nilotinib; MMR, major cytogenetic response; CCyR, complete cytogenetic response; OS, overall survival; PFS, progression-free survival; TFR, treatment-free remission; DMR, deep molecular response; TKI, tyrosine kinase inhibitor; TDM, therapeutic drug monitoring.

elderly patients with CML without increased toxicity, and every effort should be made to use standard-dose therapy in these patients to obtain the same response as in younger subjects.[21,22]

Dose Optimization Due to AEs

Although the safety profile of imatinib is superior to that of other TKIs, some patients still have intolerance to imatinib. AEs to imatinib are generally grade 1 (mild) or 2 (moderate), with the most common being superficial oedema, nausea, muscle cramps and rash.[36] According to previous studies, serious adverse events associated with imatinib are infrequent (9.3%), most often occurring in the first year of treatment and decreasing in incidence over time, with abdominal pain being the most common.[37] A previous study reported that four patients reported a reduction in the imatinib dose from 400 mg to 200 mg daily due to intolerance after achieving molecular remission, side effects subsided and BCR::ABL negativity persisted for a median of 17 months.[23] Another Korean study reported nine CML patients whose imatinib dose was reduced to 300 or 200 mg daily mainly because of severe neutropenia or thrombocytopenia (grade 3 or 4). The dose reduction resulted in a significant reduction in toxicity from Grade 3 or 4 to Grade 1 or 2, while maintaining treatment responses.[24] Therefore, reducing the dose of imatinib may help reduce the incidence of AEs.

Dose Optimization After Achieving a Stable Molecular Response

Optimally responsive patients may be overtreated with standard doses of TKIs. Therefore, TKI dose reduction should be considered for the management and prevention of AEs to improve HRQOL. In 43 patients who achieved a sustained deep molecular response (DMR) (Supplement Table 1). Over a median time of 4 years, the imatinib dose was reduced to 300 mg daily; none lost the major molecular response (MMR), and 62.2% of patients experienced improvement in toxicity.[25] Moreover, dose-halving may become a new treatment paradigm for CML patients with DMR receiving ongoing maintenance TKI therapy.[26,28,38] In particular, de-escalation treatment has shown clinical benefits over discontinuation in terms of molecular recurrence-free survival.[28]

In addition, intermittent treatment with TKIs is an option for CML patients who have an optimal response to TKIs but do not meet the current discontinuation requirements, especially elderly patients.[29,30] Although the intensification of the intermittent TKI schedule in the PROGRESSIVE arm of the OPTkIMA trial was associated with a higher incidence of MMR loss, this did not translate into an increased incidence of disease progression.[31] The progressive intermittent schedule can be regarded as a "patient selection tool" for discontinuing TKIs, as patients who maintain an MMR at the end of the study are frequently considered eligible for TFR.[31]

Dose Optimization Before TFR

Given the promising results in the treatment of CML patients with TKIs, the life expectancy of CML patients is close to that of non-CML population. TFR has become the main therapeutic target in CML to improve the quality of life of patients and reduce their financial burden.[39] Recently, Italian hematologists noted that the use of low-dose TKIs does not seem to affect the probability of achieving DMR, so attempting to discontinue treatment may even increase the TFR rate.[40,41] Compared with the EURO-SKI trial, in which full-dose treatment was discontinued after stable DMR was achieved, DESTINY had a higher recurrence-free survival rate (72% vs 50%) at 24 months, in which patients were treated with a half-dose for 1 year before discontinuation.[27,32] Most studies typically report a recurrence-free survival of 50–60% in CP-CML patients with stable DMR who have been treated with TKIs for several years.[42] Although another study also revealed a slightly higher TFR rate in the low-dose group than in the full-dose group, prospective randomized clinical trials must be undertaken to answer the controversial issue that improvement in the TFR is associated with the TKI de-escalation strategy prior to discontinuation of TKI therapy.[33] In addition, it is an attempt to achieve TFR by gradually escalating TKI treatment, and although a subgroup of patients were unsuccessful in complete discontinuation, the molecular response was maintained at a lower TKI dose.[34]

Dose Optimization of Dasatinib

Dasatinib, a 2G TKI, was approved in 2006 in the United States. Preclinical studies have shown that, compared with imatinib, dasatinib has 325-fold greater in vitro activity against native BCR::ABL and can overcome primary (intrinsic)

and secondary (acquired) imatinib resistance.[43,44] The final long-term results of the DASISION study clearly revealed that 100 mg of dasatinib QD had a faster and deeper molecular response than 400 mg of imatinib QD in newly diagnosed CP-CML patients.[45] As with imatinib, dose optimization studies of dasatinib have been ongoing, taking into account the quality of patient survival and safety issues (Table 2).

Dose Optimization in Patients with Newly Diagnosed CP-CML

With respect to the dose optimization of dasatinib, one success has been achieved by switching from 70 mg BID to 100 mg QD.[47] Recently, initial treatment with 50 mg of dasatinib QD was shown to be effective and well tolerated in newly diagnosed CP-CML patients, and it may be a new alternative choice in CP-CML.[48–51] Dasatinib 50 mg daily was at least as effective as 100 mg daily with a better safety profile and drug exposure, and the incidence rate of grade 3 to 4 pleural effusion (PE) was only 2% with a median follow-up time of 5 years.[50] In addition, early molecular response (EMR) rates were comparable between low-dose dasatinib and standard-dose imatinib, but DMR rates were significantly higher with low-dose dasatinib.[52] Similarly, reducing the dose of dasatinib below 100 mg daily (even to ≤ 20 mg daily) in elderly CML patients induced rapid and deep molecular responses without causing severe AEs.[53–55]

Dose Optimization Due to AEs

PE is one of the most frequently reported drug-related, nonhematologic AEs associated with dasatinib, and its incidence is the highest in the first year.[45] In 2013, a study reported that on/off treatment with a weekend drug holiday significantly reduced PE and hematologic toxicity without impairing the efficacy of dasatinib in imatinib-resistant and imatinib-intolerant CP-CML patients.[56] Additionally, for patients who experienced AEs, reducing the dose of dasatinib to 80 mg or 50 mg was a safe and effective treatment option.[46] Interestingly, Italian scholars Iurlo et al found through research that reducing the dose of dasatinib after the first PE event had no preventive effect on the recurrence of this AE. For patients who have already achieved MMR or DMR, reducing the dose as soon as possible before PE occurs may help to reduce the incidence of PE.[60]

Dose Optimization After Achieving a Stable Molecular Response

Multiple studies have shown that it is feasible to reduce the TKI dose (or even halve it) after a stable molecular response is achieved without affecting the TFR rate.[27,40,41] However, few studies have explored dose optimization in patients receiving first-line 2G TKIs after achieving a stable molecular response and before TFR. The DESTINY trial (n=174) included only a small number of patients receiving first-line 2G TKIs (10 patients with dasatinib and 16 patients with nilotinib).[26,27] Patients with newly diagnosed CP-CML, who received at least 24 months of dasatinib treatment and had a sustained DMR for at least 1 year, were asked to discontinue dasatinib directly in the DADI trial and DASFREE study.[57,58] These studies demonstrate that dasatinib discontinuation is a viable and potentially long-term option in patients with CML-CP. However, it is necessary to further confirm in larger-scale trials how to choose after achieving a sustained DMR: discontinue the drug or reduce the dosage.

Dose Optimization of Nilotinib

Nilotinib was approved for marketing in 2007 in the United States and was the first and only TKI approved to be discontinued.[61] Nilotinib may be preferred in patients who have a history of lung disease or are considered to be at risk for developing PE.[4] Compared with studies exploring imatinib, fewer studies have explored the dose optimization of nilotinib (Table 3).

Dose Optimization in Patients with Newly Diagnosed CP-CML

The recommended starting dose of nilotinib is 300 mg BID for patients with newly diagnosed CP-CML and 400 mg BID for those with resistant or intolerant CP-CML.[4] However, AEs were more common in the nilotinib 400 mg BID group than in the nilotinib 300 mg BID group.[62] In a retrospective study evaluating the efficacy of early dose modification in patients with newly diagnosed CP-CML, patients in the reduced group experienced better therapeutic efficacy and a lower rate of AEs than did those in the standard group.[64] In addition, in CP-CML patients intolerant to imatinib or

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Table 2 Studies of Dasatinib Dose Optimization

Study	Publication Time	Country	Types of Design	Patients	Intervention	Efficacy Endpoints	Outcome
Cortes et al[45]	2016	USA, France, Italy, et al	Clinical trial (NCT00481247)	519	DAS 100 mg vs IM 400 mg	MMR MR4.5	Cumulative rates of 5-year MMR and MR4.5 were 76% and 42% for dasatinib and 64% and 33% for imatinib, respectively (P = 0.0022 and P = 0.0251, respectively).
Cortes et al[46]	2017	USA, France, Italy, et al	Clinical trial (NCT00481247)	259	100 mg to 80 mg or 50 mg	MMR MR4	Dose reductions for any cause, including pleural effusion, did not affect efficacy (MMR rates were not reduced).
Shah et al[47]	2016	USA, UK, Italy et al	Clinical trial (NCT00123474)	670	100 mg QD vs 50 mg BID vs 140 mg QD vs 70m g BID	MMR MR4 MR4.5	During the 7-year follow-up, the MMR rates were 46%, 44%, 44%, and 46%, in the 100 mg QD, 50 mg BID, 140 mg QD, and 70 mg BID arms, respectively. Rates for MR4 and MR4.5 at any time were greatest in the 100 mg QD arm at 29% and 20%, respectively, compared with each of the other arms (50 mg BID: 21% and 13%; 140 mg QD: 23% and 11%; 70 mg BID: 22% and 14%, respectively).
Naqvi et al[48–50]	2018	USA	Clinical trial (NCT02689440)	75	50 mg	MMR MR4 MR4.5	At 12 months, 79%, 71% and 46% of patients achieved MMR, MR4.0 and MR4.5, respectively.
Jabbour et al[51]	2022	USA	Propensity score analysis	233	50 mg vs 100 mg	MMR MR4 MR4.5	The 3-year MMR rates were 92% and 84% for low-dose and standard-dose dasatinib, respectively (p = 0.23). The 3-year MR4 rates were 77% and 66% (p = 0.04). The 3-year MR4.5 rates were 77% and 62% (p = 0.02).
Ahmed et al[52]	2023	India	Observational study	50	DAS 50 mg vs IM 400 mg	MMR	At 12 months, 68% and 66.6% of patients achieved MMR with dasatinib 50 mg and imatinib 400 mg, respectively (P = 0.773).
Itamura et al[53]	2017	Japan	Retrospective study	21	<100 mg	MMR MR4 MR4.5	19%, 62%, and 96% of patients achieved MMR by 3, 6, and 12 months, respectively. 19%, 43%, and 62% of patients achieved MR4 by 6, 12, and 24 months, respectively.
Stagno et al[54]	2021	Italy	Retrospective study	45	100 mg vs 80 mg vs 50 mg	CCyR MMR DMR	93.3%, 77.7%, 53.3% of patients achieved CCyR, MMR and DMR at any time, respectively.
Murai et al[55]	2021	Japan	Clinical trial (UMIN000024548)	52	20 mg	MMR	60% of patients achieved MMR at 12 months.
La Rosée et al[56]	2013	Germany	Retrospective study	33	Weekly on/off regimen	MMR	58% of patients showed effective disease control, either demonstrated by achieving an improved response level (12/31) or keeping the response level achieved by conventional continuous dosing (6/31).
Kimura et al[57]	2020	Japan	Clinical trial (UMIN000011099)	68	Discontinuation	TFR	TFR at 6 months was 55·2%.
Shah et al[58]	2020	USA, France, Italy, et al	Clinical trial (NCT01850004)	84	Discontinuation	TFR	TFR at 2 years was 46%.
Rousselot et al[59]	2021	Canada, France	Clinical trial (NCT01916785)	287	TDM	Cumulative incidence of PE	Cumulative incidence of PE in the TDM arm compared to the control arm [4% vs 15%; 11% vs 35% and 12% vs 39% at 1, 2 and 3 years, respectively (P = 0.0094)].

Abbreviations: IM, imatinib; DAS, dasatinib; MMR, major cytogenetic response; CCyR, complete cytogenetic response; PE, pleural effusion; QD, once daily; BID, twice daily; DMR, deep molecular response; TFR, treatment-free remission; TDM, therapeutic drug monitoring.

Table 3 Studies of Nilotinib Dose Optimization

Study	Publication Time	Country	Types of Design	Patients	Intervention	Efficacy Endpoints	Outcome
Hochhaus et al[62,63]	2016	USA, Italy, Japan et al	Clinical trial (NCT00471497)	846	NI 300 or 400 mg BID vs IM 400 mg	MMR MR4.5	Cumulative 10-year rates of MMR and MR4.5 were higher with nilotinib (300 mg, BID, 77.7% and 61.0%, respectively; 400 mg BID, 79.7% and 61.2%, respectively) than with imatinib (400 mg, 62.5% and 39.2%, respectively).
Tokuhira et al[64]	2018	Japan	Retrospective study	70	300 mg BID vs. <300 mg BID	MMR MR4.5	The MMR rates were 85% and 82% in the Standard group and Reduced group, respectively ($p = 0.731$). The MR4.5 rates were 54% and 41% in the Standard group and Reduced group, respectively ($p = 0.44$).
Hiwase et al[65]	2018	Australia	Clinical trial (NCT02108951)	20	300 mg BID	MR4.5	After the switch to nilotinib 300 mg BID, MR4.5 at any time point up to month 24 was achieved 50%.
Hughes et al[66]	2017	Australia, Canada, Russian Federation et al	Clinical trial (NCT01254188)	421	300-400 mg BID	MMR	70.8% of patients achieved MMR by 12 months and 81.0% of patients achieved MMR by 24 months.
Rea et al[67]	2017	France	Retrospective study	81	300 or 400 mg BID to 300 or 400 mg QD	Loss of MMR	Only 2 patients lost MMR 4 and 6 months after QD dose reduction. None of the patients who were at least in MR4 at baseline lost MMR.
Stagno et al[61,68]	2021	Italy	Clinical trial (NCT03874858)	113	300 mg BID to 300 mg QD before discontinuation	Loss of MMR	During de-escalation, 76.9% of patients sustained DMR. Approximately 68% of patients remained TFR at 1 year after stopping nilotinib.

Abbreviations: IM, imatinib; NL, nilotinib; QD, once daily; BID, twice daily; MMR, major cytogenetic response; DMR, deep molecular response; TFR, treatment-free remission.

dasatinib, switching to nilotinib 300 mg BID was effective and well tolerated, below the recommended dose of 400 mg BID.[65]

Dose Optimization Due to AEs

The most common non-hematological AEs of nilotinib are headache, rash, and nausea.[66] Patients treated with nilotinib had more cardiovascular events and more frequent increases in blood cholesterol and glucose levels than did those treated with imatinib.[62] A total of 48.7% of patients had AEs leading to dose adjustments or interruptions and 20.9% of patients had their nilotinib dose escalated to 400 mg BID due to lack of efficacy in the ENESTxtnd.[66] Compared with ENESTnd, ENESTxtnd allows patients with insufficient response and those with drug-related AEs to have their nilotinib dose actively escalated or reduced and re-escalated, and then continue therapy, and ENESTxtnd has a higher MMR rate.[66] Therefore, it is necessary to optimize the dose individually according to the specific conditions of the patients.

Dose Optimization After Achieving a Stable Molecular Response

The NILO-RED study provided preliminary evidence that it is feasible and safe to switch to a nilotinib QD regimen at reduced doses as maintenance therapy after achieving an MMR on a standard-dose nilotinib BID schedule in CP-CML patients, regardless of prior treatment history.[67] Only 2 patients treated with first-line nilotinib lost their MMR at 4 and 6 months after the QD regimen of nilotinib, but they spontaneously recovered 4 and 6 months later.

Dose Optimization Before TFR

Although nilotinib is the first and only TKI approved for stopping therapy, a nilotinib-based TFR optimization strategy has not been formally studied. The DANTE study is the first to evaluate the safety and feasibility of nilotinib de-escalation before TFR in CP-CML patients.[61,68] A total of 107 CP-CML patients who achieved DMR for ≥1 year were enrolled, and then treated with nilotinib 300 mg QD in this study for 48 weeks. Finally, 52 patients completed de-escalation treatment, and 40 patients entered the TFR stage. De-escalation of nilotinib before a TFR attempt in CP-CML patients with a sustained DMR may be a successful dose optimization strategy.

Dose Optimization of Bosutinib

Bosutinib was approved for marketing in 2012 for patients with intolerant or resistant CP-CML, and it was approved in 2017 for the treatment of patients with newly diagnosed CP-CML. Owing to the late marketing of bosutinib, few studies on dose optimization have been conducted (Table 4), especially after a stable molecular response was reached and bosutinib was discontinued, and further attention should be given to this topic in the future.

Dose Optimization in Patients with Newly Diagnosed CP-CML

Bosutinib 400 mg daily is recommended for patients with newly diagnosed CP-CML and 500 mg daily is recommended for patients with intolerant or resistant CP-CML as second- or subsequent-line (≥ 2 L) therapy.[4] The BELA and BFORE studies are pivotal Phase III trials of bosutinib in the first-line (1 L) setting and have emphasized its improved efficacy over imatinib and the better tolerability of the 400 mg daily dose.[69,70] However, in elderly patients intolerant to or failing 1 L TKIs, bosutinib may be highly effective and better tolerated at a dose lower than 500 mg daily, even at 300 mg daily.[71]

Dose Optimization Due to AEs

In both 1 L and ≥ 2 L treatment, given that gastrointestinal (GI) toxicity often occurs early after treatment initiation, physicians often prefer to start treatment at a lower dose (200 to 300 mg) and gradually increase the dose until the patients reach either the standard 400 mg daily dose or their maximum tolerated dose.[75] The BODO study investigated the tolerability and efficacy of a step-in dosing concept of bosutinib (starting at 300 mg daily) in CP-CML patients in the ≥2 L line who were intolerant to or failed previous TKI treatment.[72] However, their data could not show that bosutinib, in which the dosing started at 300 mg daily, and toxicity-related dose adaptation led to significant improvement in early GI

Table 4 Studies of Bosutinib Dose Optimization

Study	Publication Time	Country	Types of Design	Patients	Intervention	Efficacy Endpoints	Outcome
Cortes et al[69]	2018	USA, UK, Italy et al	Clinical trial (NCT02130557)	536	BO 400 mg vs IM 400 mg	MMR CCyR	The MMR rates were 47.2% for bosutinib and 36.9% for imatinib at 12 months, respectively (P = 0.02). The CCyR rates were 77.2% for bosutinib and 66.4% for imatinib at 12 months, respectively (P = 0.0075).
Cortes et al[70]	2012	USA, Italy, Japan et al	Clinical trial (NCT00574873)	502	BO 500 mg vs IM 400 mg	MMR CCyR	The MMR rates were 41% for bosutinib and 27% for imatinib at 12 months, respectively (P<0.001). The CCyR rates were 70% for bosutinib and 68% for imatinib at 12 months, respectively (P = 0.601).
Castagnetti et al[71]	2019	Italy	Clinical trial (NCT02810990)	63	From 200 mg gradual dose increase to 300 mg or 400 mg	MMR	The cumulative rate of patients achieving or maintaining MMR by 12 months was 60%.
Isfort et al[72]	2023	Germany	Clinical trial (NCT02577926)	57	From 300 mg gradual dose increase to 500 mg	The incidence rate of grade 2 to 4 GI toxicity	The cumulative confirmed MMR rate by 1 year was 68%, the MR4 and MR4.5 rates were 43% and 26%, respectively. The incidence rates of grade 2 to 4 GI toxicity within the first 6, 12 and 24 months were 60%, 65% and 72%, respectively.
Kota et al[73]	2021	USA, Italy, Japan et al	Clinical trial (NCT00261846)	570	From 500 mg gradual dose decrease to 400 mg/300 mg/200 mg	CCyR	37% of patients achieved CCyR with bosutinib 500 mg. Bosutinib dose reduction to 400, 300, or 200 mg/day, 43%, 38%, and 43% of patients, respectively, maintained or achieved CCyR after dose reduction.
Mita et al[74]	2018	Japan	Prospective study	25	500 mg vs beginning 100 mg/day and increased by 100 mg every 2 weeks of dose escalation	Bosutinib trough plasma concentration(C_0)	At 6 months, the median C_0 was 63.7 ng/mL and 63.0 ng/mL in the standard dose and dose escalation groups, respectively.

Abbreviations: IM, imatinib; BO, bosutinib; MMR, major cytogenetic response; CCyR, complete cytogenetic response; GI, gastrointestinal.

toxicity. On the other hand, using a strategy to manage AEs with bosutinib through dose reduction from 500 mg to 400 mg or 300 mg daily can lead to improved/ maintained efficacy and better tolerability.[73]

Dose Optimization of Other TKIs

Ponatinib

Ponatinib is a potent oral bioavailable pan BCR::ABL inhibitor that is 520-fold more potent than imatinib and inhibits both wild-type and mutant BCR::ABL 1 kinases, including the "gatekeeper" T315 I mutation, with resistance to all other currently available TKIs.[76] Based on the OPTIC trial, the recommended starting dose of ponatinib is 45 mg once daily, and when patients once ≤1% BCR::ABL, the dose is reduced to 15 mg once daily to reduce the risk of cardiovascular side effects.[77,78] Indeed, anecdotal evidence suggests that clinicians start ponatinib at 45 once daily only in a few cases and most patients start treatment at 30 mg once daily.[79] The German consensus also states that some patients may consider starting ponatinib at a lower dose, and the initial dose should be determined by evaluating each individual case, considering CML disease state and patient characteristics, prior treatment, mutation status, CV risk, and therapy goals[80,81] (Table 5).

Asciminib

Asciminib is the first BCR::ABL1 inhibitor that works by Specifically Targeting the ABL1 Myristoyl Pocket (STAMP), which received accelerated approval by the US FDA for patients with CP-CML treated with≥2 prior TKIs and full approval for patients with CP-CML with the T315I mutation based on results of the Phase I study in October 2021.[84] A study showed that 40 mg BID and 80 mg QD regimens demonstrated similar and substantial efficacy with well-tolerated safety in patients without T315I mutation.[85] And the 200 mg BID dose was deemed safe and effective for patients with T315I mutation.[85] However, the ongoing ASC2ESCALATE trial pointed out dose escalation is an option for patients who do not reach response milestones in 1L and 2L[82] (Table 5).

Radotinib

Radotinib is a selective 2G BCR::ABL1 TKI that was approved by the Korean Ministry of Food and Drug Safety in 2012.[83] The approved starting dose is 400 mg BID for the treatment of patients with CP-CML resistant and/ or intolerant to imatinib, and 300 mg BID for the treatment of patients with newly diagnosed CP-CML.[83] However, a study have shown that the starting dose of radotinib adjusted for individual patients'BW (Dose/BW) at baseline was positively associated with the occurrence of dose-limiting toxicity (DLT) by 12 months of radotinib therapy,

Table 5 Studies of Other TKIs (Ponatinib, Asciminib, Radotinib) Dose Optimization

Study	Publication Time	Country	Types of Design	Patients	Intervention	Efficacy Endpoints	Outcome
Kantarjian et al[77,78]	2020	USA, UK, Korea et al	Clinical trial (NCT02467270)	276	PO 45 mg vs PO 30 mg vs PO 15 mg; receiving 45 or 30 mg/day reduced to 15 mg/day once achieving ≤1% BCR::ABL1	PFS OS	PFS and OS were 81% and 93%, respectively, in OPTIC (up to 2 years). Serious treatment-emergent AE rate was lower in OPTIC with a response-adjusted dosing regimen compared with PACE (31.2% vs 63.4%).
Atallah et al[82]	2024	USA	Clinical trial (NCT05384587)	196	Asc 80 mg, increase dose to 200mg QD if not achieved BCR::ABL1 ≤1% at 6 months	MMR	ASC2ESCALATE is an ongoing, Phase II, multicenter, single-arm, dose-escalation study of asciminib in 2L and first-line treatmen t of CP-CML.
Kim et al[83]	2014	Korea, India, Thailand	Clinical trial (NCT01602952)	77	Ra 400 mg BID	MCyR	MCyR was achieved in 50 (65%; cumulative 75%) patients, including 36 (47%) patients with CCyR by 12 months.

Abbreviations: PO, Ponatinib; Asc, Asciminib; Ra, Radotinib; MMR, major cytogenetic response; QD, once daily; BID, twice daily; OS, overall survival; PFS, progression-free survival; MCyR, Major cytogenetic response; CCyR, complete cytogenetic response.

and the probability of achieving MMR at 12 months was associated with the Dose/BW of radotinib in an inverse manner.[86,87] Therefore, they suggest 400 mg once daily be tested to patients as the 1L treatment of CP-CML, and the dose may be titrated up later as needed based on a careful monitoring of efficacy and safety responses[87] (Table 5).

TDM-Guided Dose Optimization

TKIs have shown exposure–response and exposure–safety correlations. Pharmacokinetic exposure, such as the area under the plasma concentration time curve (AUC) or the plasma trough level (C_{min}), varies highly between CML patients.[88,89] Some patients may experience treatment-related toxicity due to high exposure, whereas others may experience suboptimal reactions due to insufficient exposure.[88] Patients receiving imatinib concentrations >1685 ng/mL were more likely to develop diarrhea, whereas those receiving concentrations >1575 ng/mL were more likely to develop periorbital and limb edema.[90] Consequently, TDM is a new strategy for dose optimization to achieve faster and more effective clinical response and reduce the incidence of AEs during TKI therapy in CML patients.[91]

The implementation of TDM for TKIs requires consideration of analytical methodologies with adequate sensitivity to capture the narrow therapeutic windows of these agents. Currently, the main methods used for TDM of TKIs include liquid chromatography-tandem mass spectrometry (LC-MS/MS), high performance liquid chromatography coupled to ultraviolet detection (HPLC-UV) and enzyme-linked immunosorbent assay (ELISA).[92,93] The LC-MS/MS method enables simultaneous quantification of these TKIs and their metabolites, demonstrating high sensitivity and selectivity even at low plasma concentrations below 1 ng/mL.[92] But LC-MS/MS equipment is expensive. As clinical monitoring requires a simpler and more cost-effective method, the plasma concentrations of imatinib and nilotinib can be determined by the HPLC-UV method after comparison with the results obtained by the standard LC-MS/MS method.[92] And the cost of each sample for this HPLC-UV method used to determine imatinib and nilotinib is approximately $4, including running costs.[92] However, in the quantification of dasatinib, the highly sensitive LC-MS/MS method is superior to the HPLC-UV method. Because the quantification limit of dasatinib plasma concentration is less than 1.0 ng/mL (approximately 0.1ng/mL).[92] The application of immunoassay in TKI-TDM is relatively limited. At present, only a few TKIs (such as imatinib) have commercially available immunoassay kits, which use the principles of chemiluminescence immunoassay (CLIA) or ELISA.

Rousselot et al conducted studies of imatinib and dasatinib to evaluate the value of dose optimization on the basis of monitoring C_{min} levels in patients with newly diagnosed CP-CML.[35,59] They divided patients into TDM arms, control arms, and observation arms on the basis of the C_{min} level and treated them with different dosing strategies. The results showed that TDM served as a valuable "PE prediction tool" for dasatinib. A similar study was conducted with bosutinib: the daily dose of bosutinib might be adjusted on the basis of the target C_0 to avoid AEs in general clinical practice.[74] These results provide initial indications of the clinical benefits of TDM in individualized medication to optimize outcomes for each patient.

Effect of Dose Optimization on HRQOL

HRQOL is an important therapeutic goal of molecular targeted therapy for patients with CML. Fatigue, gastrointestinal reactions, edema, rash, and skeletal muscle soreness are frequent symptoms among CML patients.[94] Previous studies have shown that chronic fatigue is a major factor limiting HRQOL in CML patients treated with imatinib.[95] A study in a Chinese population analyzed the effect of TKI treatment on HRQOL via online questionnaires, 45.0% reported a slight effect, 28.8% reported a moderate impact, 13.1% reported slight impact, 2.4% reported a severe impact, and only 10.6% reported no impact.[94] In addition, they concluded that full-dose TKI therapy and a history of TKI intolerance were significantly associated with poor HRQOL.[94]

Luo et al reported that there was no significant difference in overall health status scores ($P = 0.889$) between de-escalation group and discontinuation group, but emotional functioning tended to be worse in the discontinuation group ($P = 0.038$).[28] Among the four items related to emotional function, tension and trepidation of disease are the most common emotional responses in CML patients, especially people in the discontinuation cohort had a higher prevalence and more moderate or

severe tension and trepidation of disease than did those in the de-escalation cohort.[28] Compared with TKI discontinuation, TKI dose reduction significantly improved patients' HRQOL and mental health.[28,94] Most patients indicate that they prefer dose reduction before stopping TKI therapy because they fear disease relapse.[28,94] Similarly, HRQOL gradually improved with intermittent schedules in elderly CML patients.[30,31]

Conclusions

The primary goal of dose optimization is to maintain the proven efficacy of TKIs at the lowest possible dose and reduce AEs. Most studies have shown that dose optimization can indeed reduce the incidence of AEs and improve quality of life.

Dose optimization may be considered at all stages of the patients' treatment journey. For newly diagnosed patients, the standard or low dose of initial treatment can be considered according to the patient's age and physical function. In the course of treatment, if there are serious AEs, the dose should be reduced or discontinued according to the specific circumstances. When patients achieve a stable molecular response, they may choose to maintain therapy with a low dose of TKI or discontinue the drug after qualifying for discontinuation. Molecular responses should be closely monitored during dose optimization, and the original treatment regimen should be immediately restored if molecular relapse occurs.

Dose optimization on the basis of TDM may help improve patient effectiveness and reduce AEs, so the inclusion of TDM as an important part of TKI therapy is suggested. Furthermore, the HRQOL of CML patients after dose optimization is another area that needs to be focused on. Novel prospective clinical trials and real-life clinical practices are still needed to explore dose optimization of CP-CML as a new promising treatment strategy, which will lead to further improvements in quality of life and outcomes for CP-CML patients.

Data Sharing Statement

Data sharing is not applicable to this article because no new data were created or analyzed in this study.

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