Review

Therapeutic Drug Monitoring of Imatinib, Nilotinib, and Dasatinib for Patients with Chronic Myeloid Leukemia

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Imatinib, nilotinib, and dasatinib are tyrosine kinase inhibitors (TKIs) that have become first-line treatments for Philadelphia chromosome-positive chronic myeloid leukemia (CML). According to European LeukemiaNet recommendations, the clinical response of CML patients receiving TKI therapy should be evaluated after 3, 6, and 12 months. For patients not achieving a satisfactory response within 3 months, the mean plasma concentration for the three months of TKI administration must be considered. In TKI therapy for CML patients, therapeutic drug monitoring is a new strategy for dosage optimization to obtain a faster and more effective clinical response. The imatinib plasma trough concentration (\(C_0\)) should be set above 1000 ng/mL to obtain a response and below 3000 ng/mL to avoid serious adverse events such as neutropenia. For patients with a \(UGT1A1^*6/6, *6/28, \) or \(*28/28\) genotype initially administered 300–400 mg/d, a target nilotinib \(C_0\) of 500 ng/mL is recommended to prevent elevation of bilirubin levels, whereas for patients with the \(UGT1A1^*1\) allele initially administered 600 mg/d, a target nilotinib \(C_0\) of 800 ng/mL is recommended. For dasatinib, it is recommended that a higher \(C_{\text{max}}\) or \(C_2\) (above 50 ng/mL) to obtain a clinical response and a lower \(C_0\) (less than 2.5 ng/mL) to avoid pleural effusion be maintained by once daily administration of dasatinib. Although at present clinicians consider the next pharmacotherapy from clinical responses (efficacy/toxicity) obtained by a fixed dosage of TKI, the TKI dosage should be adjusted based on target plasma concentrations to maximize the efficacy and to minimize the incidence of adverse events.

**Key words** imatinib; nilotinib; dasatinib; therapeutic drug monitoring

1. INTRODUCTION

Imatinib, nilotinib, and dasatinib are tyrosine kinase inhibitors (TKIs) that have become first-line treatments for Philadelphia chromosome-positive chronic myeloid leukemia (CML).

According to European LeukemiaNet (ELN) recommendations, the clinical response of CML patients should be evaluated 3, 6, and 12 months after initiating these TKI therapies. An optimal response is defined as a BCR-ABL transcript level \(\leq 0.1\%\) to avoid pleural effusion be maintained by once daily administration of dasatinib. Although at present clinicians consider the next pharmacotherapy from clinical responses (efficacy/toxicity) obtained by a fixed dosage of TKI, the TKI dosage should be adjusted based on target plasma concentrations to maximize the efficacy and to minimize the incidence of adverse events.

Therapeutic drug monitoring (TDM) is carried out by evaluating the drug concentration in biological fluids to provide individual treatment through dose-adjustment to improve efficacy or avoid adverse events and to transition from an ineffective treatment to a clinical effect. However, to carry out TDM, therapeutic target ranges indicating exposure-response (efficacy/toxicity) relationships must be determined. For patients who do not achieve a CCyR or MMR at each time point, the plasma concentration of these TKIs must be adequately considered, and mutations in the BCR-ABL kinase domain should also be analyzed. TDM is considered a dosing optimization tool to obtain faster clinical responses such as CCyR or MMR with TKIs. The aim of this paper is to review the exposure–response relationships of imatinib, nilotinib, and dasatinib from our previous studies and to describe new strategies for pharmacotherapy in CML treatment to avoid unnecessary complications and potentially achieve a cure.

2. IMATINIB TDM

After oral administration, imatinib is rapidly and completely absorbed with a bioavailability of 98.3%,\(^7\) after which it is extensively metabolized to the \(N\)-desmethyl derivative CGP74588 (\(N\)-desmethylimatinib) by CYP 3A4,\(^8,9\) and up to 80% of the administered dose is excreted in the feces as metabolites or unchanged drug by the agency of ATP-binding cassette (ABC) transporters, such as the breast cancer resistance protein (BCRP) or P-glycoprotein.\(^10\) In addition to inter-patient variability of the activity of enzymes or transporters related to imatinib pharmacokinetics, factors such as age, gender, body size, liver, and renal function, drug interactions, and adherence to therapy are also causes of individual differences in imatinib plasma concentration.\(^10\) Consequently, the steady-state plasma trough concentration (\(C_0\)) of imatinib obtained 24h after administration of a 400 mg standard daily dose ranged from 109 ng/mL to 4980 ng/mL,\(^11–20\) and ranged from 140 ng/mL to 2457 ng/mL when limited to Japanese CML patients.\(^21–26\) In Japanese CML patients, the inter-patient imatinib \(C_0\) coefficient of variation (CV) ranged from 38.2% to 62.9%.\(^21–25\) Several studies have investigated whether the imatinib \(C_0\) reflects the clinical response of patients taking imatinib, namely exposure–response relationships.\(^11,12,20–22,25–30\) In Japanese CML patients, we have reported that the imatinib \(C_0\) was significantly higher in patients with a MMR than in those without a MMR, the mean values were 1107±594 ng/mL and 873±529 ng/mL, respectively (\(p=0.002\)).\(^23\) Picard et al. first reported that a steady-state imatinib \(C_0\) measured after at least 12 months of treatment with a standard imatinib dose correlated with the MMR, and the threshold for the ima.
tinib $C_0$ should be set above 1002 ng/mL. Several studies have also reported that patients with an imatinib $C_0$ less than 1000 ng/mL have a significantly lower rate of successfully achieving an improved MMR. In the combined data set, the rate of MMR achievement was significantly higher for patients with an imatinib $C_0$ above 1000 ng/mL than for patients with a $C_0$ less than 1000 ng/mL (odds ratio, 2.48; 95% CI, 1.82–3.38, $p < 0.0001$) (Fig. 1). Thus, for CML patients, the target imatinib $C_0$ should be set above 1000 ng/mL.

However, dose adjustment according to the target concentration should not be evaluated with an imatinib $C_0$ of only one point, for example only days 28 or 29 after beginning imatinib treatment, because variability of the intra-patient imatinib $C_0$ CV is quite large ranging from 8.4% to 49.3%. Therefore, a recommendation for the measurement of imatinib $C_0$ is each week for the first month after beginning treatment, then once a month to month three, and subsequently every three months up to one year with appropriate dosage adjustment. As provisionally defined by the ELN, simultaneous with an evaluation of clinical response according to transcript levels at each time point, the mean imatinib $C_0$ for three months or using multiple points should also be assessed for each patient treated with imatinib (Fig. 2). After one year, the imatinib $C_0$ might be assessed at 6-month intervals, as well as each time a potentially interacting drug is introduced or withdrawn or if poor adherence to treatment is suspected.

Patients with a mean imatinib $C_0$ above 1000 ng/mL not exhibiting a positive effect (non-responders) might switch to a 2nd generation TKI therapy such as nilotinib or dasatinib (Fig. 3). On the other hand, non-responders with a mean imatinib $C_0$ less than 1000 ng/mL should be advised to increase the dosage from 400 mg to 600 mg (500 mg in Japanese patients because of their smaller body mass index) once daily after checking for compliance of imatinib usage, and their imatinib $C_0$ should again be monitored (Fig. 3). Patients with a mean imatinib $C_0$ less than 1000 ng/mL that have intolerable toxicities such as edema and rash should also switch to a 2nd generation TKI, whereas patients with a mean imatinib $C_0$ above 1000 ng/mL with intolerable toxicities might suspend imatinib administration and then restart treatment at a 100 mg

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**Fig. 1.** Meta-analysis for Correlation between Imatinib $C_0 >$1000 ng/mL and MMR

**Fig. 2.** A Therapeutic Strategy for CML Patients Treated with Imatinib

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Dr. Masatomo Miura was born in Fukushima in 1970. After graduating from the Faculty of Pharmaceutical Sciences at Tohoku Pharmaceutical University in 1992, he graduated from the Graduate School of Pharmaceutical Sciences at that university in 1994 under the supervision of Professor Mitsushiro Takeshita. He then worked as Assistant Professor for Professor Takeshita in the Department of Pharmacetics and in 2000, and obtained a Ph.D. degree from the university. In 2000, he moved to the Department of Pharmacy at Hirosaki University Hospital, where he studied clinical pharmacokinetics under the supervision of Associate Professor Tadashi Ohkubo. In 2002, he joined the Department of Pharmacy at Akita University Hospital, where he was appointed Associate Professor and Director in 2009, subsequently being appointed Professor and Director in 2013. He was awarded the Pharmaceutical Society of Japan Award in the Tohoku Block for Young Scientists in 2005, the 4th Japan Research Foundation for Clinical Pharmacology Research Award in 2011, and the Sato Memorial Award in 2015.
According to results from the previous 14 reports, the mean steady-state imatinib $C_0$ obtained 24 h after taking a 400 mg standard daily dose was 1226 ng/mL, which is greater than the 1000 ng/mL target concentration. However, patients obtaining an imatinib $C_0$ above 1000 ng/mL administered the lower dose of 200 mg were very rare. The overall survival (OS) and event-free survival (EFS) was reported to be significantly inferior for patients taking an imatinib dose of 200 mg compared to patients taking 400 mg and 300 mg during the same period. In the same report, the estimated cumulative rate of CCyR or MMR during the first 18 months was significantly lower for patients taking the 200 mg daily dose than for patients in the 400 mg or 300 mg groups. Even for patients intolerant of the 300–400 mg dose of imatinib, excessive dose reductions to $\leq 200$ mg imatinib should be avoided, and such patients should be switched to a 2nd generation TKI.

A complete molecular response (CMR) is defined as $\leq 0.0032\%$ of BCR-ABL 1 transcript levels. A duration of CMR more than 24 months indicates the feasibility of discontinuing imatinib therapy. Although the imatinib $C_0$ was significantly higher in patients with MMR achievement than in patients without a MMR, there was no significant difference in the imatinib $C_0$ between patients achieving or not achieving a CMR (1243±660 ng/mL vs. 1372±654 ng/mL, respectively). Furthermore, it has also been reported that there was no significant difference in the intracellular concentration of imatinib and in agreement with the findings reported by Kim et al. On the other hand, BCRP also contributes to the extracellular excretion of imatinib, and the drug efflux activity of BCRP is influenced by this SNP. Fifty-four percent of patients achieving CMR had the $ABCG2$ 421 A allele, whereas 67% of patients not achieving CMR had the $ABCG2$ 421 C/C genotype. Thus, CML patients with the $ABCG2$ 421 A allele were associated with a higher imatinib $C_0$ than patients with the 421C/C genotype. On the other hand, BCRP also contributes to the extracellular excretion of imatinib, and the drug efflux activity of BCRP is influenced by this SNP. Fifty-four percent of patients achieving CMR had the $ABCG2$ 421 A allele, whereas 67% of patients not achieving CMR had the $ABCG2$ 421 C/C genotype. Thus, CML patients with the $ABCG2$ 421 A allele were better able to achieve a CMR than patients with the 421C/C genotype. This result is believed to be associated with the intracellular concentration of imatinib and is in agreement with the findings reported by Kim et al. In addition, several studies have reported that the $ABCG2$ 421 A allele is associated with a significantly higher rate of MMR.

The involvement of multiple human transporters in imatinib pharmacokinetics makes the investigation of imatinib transport mechanisms difficult. However, among the various drug-transporters, BCRP appears to impart the strongest influence on imatinib exposure and clinical response. Knowledge of a patient’s $ABCG2$ 421C>A genotype before initiating therapy could be useful when making dosing decisions aimed at achieving optimal imatinib exposure, and in conjunction with TDM could aid patient management.

BCRP, encoded by the $ABCG2$ gene, is a membrane efflux transporter normally expressed in the small intestine and biliary canalicular front of hepatocytes, which is involved in the absorption, distribution, and excretion of a wide variety of clinically relevant drugs. The single-nucleotide polymorphism (SNP) 421C>A in the $ABCG2$ gene reduces BCRP function. The level and function of $ABCG2$ expressed from the 421 A allele are reduced compared with those of the 421C/C protein. We have reported that the dose-adjusted imatinib $C_0$ was significantly lower in Japanese patients with the $ABCG2$ 421C/C genotype than in patients with the C/A+A/A genotypes. Petain et al. have also reported that imatinib clearance in patients carrying the $ABCG2$ 421C/A genotype was significantly lower than in those subjects with the 421C/C genotype. Patients with the $ABCG2$ 421 A allele were associated with a higher imatinib $C_0$ than patients with the 421C/C genotype. On the other hand, BCRP also contributes to the extracellular excretion of imatinib, and the drug efflux activity of BCRP is influenced by this SNP. Fifty-four percent of patients achieving CMR had the $ABCG2$ 421 A allele, whereas 67% of patients not achieving CMR had the $ABCG2$ 421C/C genotype. Thus, CML patients with the $ABCG2$ 421 A allele were better able to achieve a CMR than patients with the 421C/C genotype. This result is believed to be associated with the intracellular concentration of imatinib and is in agreement with the findings reported by Kim et al. In addition, several studies have reported that the $ABCG2$ 421 A allele is associated with a significantly higher rate of MMR.

At the recommended dose of 400 mg/d, imatinib sometimes causes severe adverse events, such as neutropenia, edema, and skin rash, which in turn may lead to poor compliance, premature cessation of treatment, or failure of the therapy.
On the other hand, increased imatinib dosages above 400 mg/d have been associated with increased rates of some adverse events, and discontinuation rates of imatinib therapy were significantly greater for patients taking the higher dosage (71% vs. 44%). An imatinib C₀ above 3180 ng/mL is reported to be associated with a higher frequency of grade 3/4 adverse events such as neutropenia. With an increase in imatinib C₀, the frequency of adverse events such as rash and edema is increased. Therefore, an imatinib C₀ greater than 3000 ng/mL should be avoided.

The inter- and intra-individual variation of imatinib C₀ is very large. Therefore, a TDM should be routinely provided to CML patients taking imatinib. For CML patients that have an imatinib C₀ of 1000 ng/mL but lack a sufficient clinical response, switching to another tyrosine kinase inhibitor such as nilotinib or dasatinib is recommended.

3. NILOTINIB TDM

Nilotinib, which inhibits BCR-ABL1 with about 25-fold greater potency than imatinib, dosed at 150 mg twice daily and 200 mg twice daily gives a faster and more pronounced response compared with imatinib 400 mg once daily. Nilotinib is absorbed with a bioavailability of approximately 30%, and is metabolized by CYP3A4. Nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), potentially increasing the concentrations of drugs eliminated via UGT1A1, thereby increasing bilirubin levels.

The most common promoter sequence for UGT1A1 contains the (TA)6TAA sequence, while the less frequent *28 genotype is associated with unusually high bilirubin levels. The UGT1A1*6 (211G>A) isoform has also been reported to cause a reduction in UGT1A1 enzyme activity. In the Japanese population, the UGT1A1*6/*6, *6/*28 and *28/*28 genotypes that include activity-reducing polymorphisms were detected in 1.3%, 3.2%, and 2.7% of the population, respectively. In clinical studies, the inhibitory effect of UGT1A1 by nilotinib is particularly apparent in patients who are poor metabolizers (PMs) with the UGT1A1*6/*6, *6/*28, and *28/*28 genotypes. Singer et al. reported that patients with the UGT1A1*28/*28 genotype have an elevated risk of nilotinib-induced hyperbilirubinemia compared with patients with the extensive metabolizer (EM) genotypes such as UGT1A1*1/*1 and *1/*28, and the relative risk for grade 3 or greater hyperbilirubinemia in chronic phase CML patients with the UGT1A1*28/*28 genotype is 18 (95% CI: 4.1, 78.5). In Japanese CML patients, within the first 12 weeks of nilotinib administration, elevation of bilirubin levels in patients with UGT1A1 EM genotypes were slightly higher by 30%; however, the median time to elevation of bilirubin levels in patients with the UGT1A1 PM genotypes was 2 weeks (hazard ratio, 6.11; p=0.004). Thus, the influence of UGT1A1 inhibition by nilotinib appears within 1–3 weeks after initiating nilotinib administration. Therefore, patients with an increased risk of hyperbilirubinemia could be identified by prospective genotyping of UGT1A1 prior to initiation of nilotinib therapy. For patients with the UGT1A1*6/*6, *6/*28, or *28/*28 genotypes, reduction of the initial dose of nilotinib to 150 mg twice daily or 200 mg twice daily is necessary to prevent elevation of bilirubin levels or alternatively choosing another tyrosine kinase inhibitor such as dasatinib might be recommended (Fig. 4).

In the ENEStnd study, patients with a higher nilotinib C₀ tended to have lower BCR-ABL1 ratios at 12 months compared to patients with a lower C₀, but the difference was not statistically significant. Consequently, there was also no relationship between nilotinib C₀ and the MMR rate at 12 months after initiation of nilotinib therapy. However, in the study of patients with imatinib-resistant or -intolerant CML, patients with a lower nilotinib C₀ had a significantly longer time to CCyR (p=0.010) and MMR (p=0.012). Patients with a nilotinib C₀ above 500 ng/mL required a significantly shorter time

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**Fig. 4. A Proposed Therapeutic Strategy Using Nilotinib TDM for CML Patients**

- **Before administration**
  - UGT1A1 genotyping
  - *1/*1, *1/*6, *1/*28 genotype
  - 600 mg/day BID (1st line, 2nd line)
  - Initial dose
  - Target C₀ 800 ng/mL

- **After administration**
  - TDM
  - 300-400 mg/day BID
  - Dasatinib

- **Target C₀ 500 ng/mL**
to achieve CCyR or MMR. Similar to imatinib, therapeutic drug monitoring to maintain a target plasma concentration would be beneficial during nilotinib therapy.

In the East Japan CML (EJCML) study of 30 Japanese patients with imatinib-resistant or intolerant CML, we reported that the nilotinib \( C_0 \) was significantly higher in 21 patients with a MMR by 12 months than in 9 patients not achieving a MMR; the mean nilotinib \( C_0 \) values (median) were 1451±741 (1255) ng/mL and 534±409 (373) ng/mL, respectively (\( p=0.001 \)). The threshold for nilotinib \( C_0 \) should be set above 761 ng/mL on a receiver operating characteristic (ROC) curve with a sensitivity of 76.2% and specificity of 77.8%. Afterwards, however, 10 patients during the first 12 months discontinued nilotinib treatment because of severe adverse events such as thrombocytopenia and hyperbilirubinemia. Consequently, in the final analysis of the EJCML study, the nilotinib \( C_0 \) tended to increase in patients who achieved MMR at 12 months, but this result was not statistically significant; the median \( C_0 \) were 774 ng/mL and 490 ng/mL (less than 500 ng/mL), respectively (\( p=0.261 \)). Shibata et al. have reported that UGT1A1 SNPs are important determinants of severe toxicity from nilotinib in Japanese patients. In addition, Kim et al. suggested that decreased UGT1A1 function by nilotinib leading to decreased glucuronidation of UGT1A1 substrates might result in unexpected toxicity. In the EJCML study, we did not carry out genotyping of UGT1A1 prior to initiation of nilotinib therapy. If only UGT1A1 EM patients had been enrolled in this study, the relationship between nilotinib exposure and clinical response would be clearer.

In common practice, the daily dose of nilotinib during the maintenance phase after 3 months of nilotinib therapy for UGT1A1 PM patients was 300–400 mg/d, lower than the mean daily dose of 600 mg/d for UGT1A1 EM patients. For UGT1A1 PM patients who achieved MMR, the steady-state mean \( C_0 \) of nilotinib was 591 ng/mL. Therefore, for UGT1A1 PM CML patients, after administration of the initial 300–400 mg/d dose of nilotinib, the target nilotinib \( C_0 \) should be 500 ng/mL, although a longer time to achieve MMR might be needed (Fig. 4). Similar to our study, in a case study, Kim et al. also reported that the daily maintenance dose of nilotinib in UGT1A1 PM patients was reduced to 400 mg/d because of hyperbilirubinemia. Nilotinib should not be given above 600 mg daily for UGT1A1 PM patients. On the other hand, in UGT1A1 EM patients who achieved MMR at 12 months, the steady-state mean nilotinib \( C_0 \) was 934 ng/mL. Based on the EJCML study and the steady-state mean nilotinib \( C_0 \) of 800 ng/mL, a target \( C_0 \) of 800 ng/mL is recommended for TDM after administration of the initial 600 mg/d dose of nilotinib (Fig. 4). In UGT1A1 PM patients, the incidence of grade 3/4 hyperbilirubinemia at a nilotinib \( C_0 \) of 800 ng/mL is approximately 50%. Furthermore, continuous administration of the 600 mg/d dose of nilotinib for UGT1A1 PM patients should be avoided. If nilotinib is the initial therapy chosen for UGT1A1 PM patients, a target nilotinib \( C_0 \) of 500 ng/mL is recommended to balance efficacy and toxicity. Poor nilotinib exposure is considered to be the major contributing factor to therapeutic failure.

Similar to imatinib, dose-adjustment according to the target concentration should not be evaluated using only a single nilotinib \( C_0 \) data point, for example only day 8 after beginning treatment, because the intra-patient variability of the CV value of nilotinib \( C_0 \) is very large (mean value: 36.4%), and the bioavailability of nilotinib is increased when given with a meal. Therefore, the timing of nilotinib \( C_0 \) measurements should be the same as for imatinib after beginning treatment. Transitions of nilotinib \( C_0 \) of two patients with poor adherence to treatment are shown in Fig. 5. Thus, dose-adjustment based on the target concentration or evaluation of nilotinib \( C_0 \) for adherence to treatment requires multiple \( C_0 \) values before the evaluation time point. Therefore, it is recommended that the nilotinib \( C_0 \) be measured each week for the first month after beginning treatment, then monthly until month three, and subsequently once every three months. The periodic measurement of nilotinib \( C_0 \) might lead to the feasibility of discontinuing nilotinib in the future.

4. DASATINIB TDM

The elimination half-life of dasatinib, an inhibitor of BCR-ABL1 with a potency 325-fold that of imatinib, is approxi-

![Fig. 5. Transition of Nilotinib $C_0$ for Two Patients with Poor Adherence to Treatment](Image)
In the Dasatinib versus Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia (DASISION) trial, the rates of CCyR and MMR for dasatinib dosed 100 mg once daily were higher and showed both a faster and more pronounced response than imatinib 400 mg dosed once daily.\textsuperscript{4,66} However, all grade pleural effusion occurred in 19% of patients receiving dasatinib within 36 months, and this side effect was linked to an overall discontinuation rate of 29%.\textsuperscript{57} Wang et al. have reported that the major cytogenetic response was significantly associated with the weighted average steady-state dasatinib plasma concentration, and pleural effusion was significantly associated with the dasatinib \(C_0\) (hazard ratio 1.22) with the hazard ratio increasing 1.22-fold for every 1.0 ng/mL increase in dasatinib \(C_{\text{tr}}\).\textsuperscript{64} In the Phase I and Phase II studies, pleural effusion was reported to be less frequent with once daily dasatinib treatment than with twice daily treatment.\textsuperscript{68} In the Phase III study, the mean steady-state dasatinib \(C_0\) after taking 100 mg once daily was 2.61 ng/mL (pleural effusion rate: 11.0%), whereas with dosing 140 mg twice daily the dasatinib \(C_0\) was 6.71 ng/mL (pleural effusion rate: 22.0%).\textsuperscript{64} Yu et al. have reported that the dasatinib \(C_0\) should not exceed 2.5 ng/mL, because of increased risk of cumulative incidences of pleural effusion.\textsuperscript{69} From these previous reports, the administration of dasatinib 100 mg once daily was found to be the best dosage to obtain sufficient efficacy with reduced side effects.\textsuperscript{64,68,70} Thus, in contrast to imatinib and nilotinib, the main purpose of TDM of dasatinib is the avoidance of side effects (Fig. 6).

The frequencies of developing a T315I BCR-ABL1 mutation in patients receiving imatinib, nilotinib, and dasatinib therapy were 1.5% by 48 months, 3.3% by 48 months, and 7.1% by 36 months, respectively, and the frequency of the T315I mutation was highest in dasatinib therapy. In Philadelphia chromosome-positive acute lymphoid leukemia patients undergoing dasatinib monotherapy, we reported that the plasma concentration at 2 h (\(C_2\)), maximum plasma concentration (\(C_{\text{max}}\)), and area under the observed plasma concentration–time curve (\(AUC\)) of dasatinib were significantly lower in patients with the T315I mutation than those without this mutation.\textsuperscript{71} Therefore, it is recommended that the dasatinib \(C_2\) or \(C_{\text{max}}\) target concentration be set above 50 ng/mL to avoid a low exposure of dasatinib because of the risk of developing BCR-ABL point mutations\textsuperscript{71} (Fig. 6). An effective transient dasatinib concentration of 100 nm (approximately 50 ng/mL) is sufficient to inhibit \textit{in vitro} proliferation of most cell lines expressing imatinib-resistant BCR-ABL mutations, with the exception of T315I.\textsuperscript{72} In addition, Vainstein et al. have reported that a higher inhibitory potential at maximum concentration based on the IC\textsubscript{50} and \(C_{\text{max}}\) of dasatinib correlated with improved CCyR rates in CML patients treated with dasatinib.\textsuperscript{73} Although continuous dasatinib exposure for 24 h is not needed, a higher \(C_{\text{max}}\) of dasatinib is necessary (Fig. 6). Consequently, the therapeutic target of dasatinib is recommended to maintain a \(C_{\text{max}}\) or \(C_2\) (above 50 ng/mL) and lower \(C_0\) (less than 2.5 ng/mL) by administration of dasatinib 100 mg once daily (Fig. 6). Dose-adjustment up or down in 20 mg increments based on the target concentration or clinical response may be carried out, using once daily administration as a general rule.

In the prospective OPTIM dasatinib trial with patients newly diagnosed with CP-CML that began therapy with dasatinib 100 mg once daily, Rousset et al. reported that when patients with a dasatinib \(C_0 \geq 3 \text{ nm} (1.5 \text{ ng/mL})\) at day 15 were randomized into either a no dose-adjustment group or a dose-adjustment group to obtain a \(C_0\) of \(< 3 \text{ nm} (\text{median} \ C_0 \text{ from 5.1 nm to 2.1 nm})\), discontinuation rates of dasatinib therapy were 27% and 13%, respectively, and the overall rates of pleural effusion by 36 months were 48.9% and 11.3%, respectively (\(p = 0.008\)).\textsuperscript{74} In the same report, they also reported that the dasatinib \(C_{\text{max}}\) was found to be associated with clinical response and that the \(C_0\) was associated with fluid retention and pleural effusion.\textsuperscript{74} Thus, a dasatinib \(C_0\) not detectable in analysis by LC-MS/MS or HPLC with a limit of quantification (LOQ) of 1.0 ng/mL may signify a better clinical outcome.

Although \(AUC\) is the best pharmacokinetic parameter to characterize dasatinib exposure, many blood collection time-points are required to accurately calculate \(AUC\) values. The \(C_2\) point of dasatinib was able to accurately predict the \(AUC\) of dasatinib in a shorter time frame and could be used to predict

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{dasatinib_concentrations.png}
\caption{Target Plasma Concentrations of Imatinib, Nilotinib, and Dasatinib for CML Patients}
\end{figure}
and acid suppressants requires monitoring of the dasatinib C₀. It is recommended that a higher C₀ be set above 1000 ng/mL and less than 3000 ng/mL. BCRP appears to impart the strongest influence on imatinib exposure and clinical response. Knowledge of the ABCG2 421C→A genotype before initiating imatinib therapy would be useful for making dosing decisions aimed at achieving optimal imatinib exposure. The nilotinib C₀ after administration of an initial 300–400 mg/d dose for patients with the UGT1A1*6/*6, *6/*28, or *28/*28 genotypes would be a target C₀ of 500 ng/mL to prevent elevation of bilirubin levels, whereas for patients with the UGT1A1*1 allele, the nilotinib C₀ after administration of an initial 600 mg/d dose is recommended to give a target C₀ of 800 ng/mL. For dasatinib, it is recommended that a higher Cₘₐₓ, or C₂ (above 50 ng/mL) and lower C₀ (less than 2.5 ng/mL) be maintained by administration of dasatinib 100 mg once daily. Although at present clinicians consider the next pharmacotherapy from clinical responses such as efficacy or adverse events obtained from a fixed dosage of TKI, we suggest that the drug dosage be adjusted based on target concentration to maximize efficacy and minimize the incidence of adverse events. Consequently, TKI therapy could be continued for a longer time, and faster and more pronounced clinical responses could be obtained.

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