Therapeutic Drug Monitoring of Imatinib for Chronic Myeloid Leukemia Patients in the Chronic Phase

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Key Words

Imatinib · Therapeutic drug monitoring · Breast cancer resistance protein

Abstract

Imatinib is approved as a first-line treatment for Philadelphia chromosome-positive chronic myeloid leukemia (CML). Because of the variability in imatinib exposure among patients, therapeutic drug monitoring to maintain a plasma threshold level of about 1,000 ng/ml would be beneficial during imatinib therapy. Imatinib pharmacokinetics are influenced by body weight, comedication and pharmacogenetic factors, and the drug is excreted into the bile by the breast cancer resistance protein (*ABCG2* gene). To attain the plasma threshold of approximately 1,000 ng/ml, the daily dose for patients with the *ABCG2* 421C/C genotype should be 400 mg; for patients with the 421C/A or 421A/A genotype, the dose should be 300 mg. Knowledge of the *ABCG2* 421 genotype could be useful when making dosing decisions aimed at achieving the optimal imatinib exposure. A therapeutic drug monitoring service should be routinely provided to CML patients taking imatinib. For CML patients who have an imatinib trough level of 1,000 ng/ml but lack a sufficient clinical response, switching to another tyrosine kinase inhibitor is recommended.

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Introduction

Imatinib mesylate (Glivec®; Novartis, Basel, Switzerland), an inhibitor of BCR-ABL tyrosine kinase activity, has become the standard treatment for Philadelphia chromosome-positive chronic myeloid leukemia (CML), due to its demonstrated clinical efficacy and ability to produce a durable response and prolonged survival [1, 2]. However, despite its outstanding efficacy, nearly 20% of patients who take imatinib do not achieve a complete cytogenetic response (CCyR), which is the major objective of therapy and is associated with prolonged survival [3, 4]; moreover, some patients develop intolerable side effects or drug resistance over time [5]. A major molecular response (MMR) is also considered an important therapeutic target [5]. The probability of loss of CCyR within 7 years is only 3% among patients with an MMR at 18 months versus 26% among patients with CCyR but no MMR [6].

Factors that may be associated with a suboptimal response to imatinib and treatment failure include: (i) biological factors, such as the baseline presence or later emergence of a BCR-ABL mutation or other genetic variant [7, 8], or mutation of a drug influx transporter involved in the intracellular uptake of the drug [9, 10]; (ii) clinical features, such as the disease status of the patient

Fig. 1. Schematic representation of the transport and metabolism of imatinib. After oral administration, imatinib is absorbed and interacts slightly with P-glycoprotein (P-gp) at the membrane of intestinal epithelial cells and is then transported to the intestinal lumen. Upon reaching the liver, imatinib is transported into hepatocytes by organic cation transporter 1 (OCT1), where it may undergo metabolism to N-desmethylimatinib by hepatic cytochrome P450 (CYP) 3A4. A portion of the imatinib and N-des-

methylimatinib is then glucuronidated to O- or N-glucuronides by UDP-glucuronosyltransferases. Transport out of the hepatocytes into the bile occurs via breast cancer resistance protein (BCRP), which is located at the hepatocyte apical membrane. Imatinib and N-desmethylimatinib glucuronides are excreted into the bile and may undergo enterohepatic recirculation and reconversion to imatinib and N-desmethylimatinib by colonic bacterial glucuronidases. The oral bioavailability of imatinib is 98.3%.

or the Sokal risk score at baseline [11], and (iii) pharmacokinetic factors, such as drug metabolism or transport, drug-drug interactions [12, 13] and adherence [14]. In this article, we review the factors affecting imatinib exposure, in particular drug transporter polymorphisms, as well as the clinical significance of therapeutic drug monitoring of imatinib.

Pharmacokinetics

After oral administration, imatinib is rapidly and completely absorbed with an oral bioavailability of 98.3% [15], after which it is extensively metabolized, and up to 80% of the administered dose is recovered in the feces as metabolites or unchanged drug [16] (fig. 1). The mean plasma half-life of imatinib is 13.5–18.2 h [15–18]. Imatinib and its metabolites are excreted predominantly via the biliary-fecal route [16] by the ATP-binding cassette (ABC) transporters, breast cancer resistance protein (BCRP) and P-glycoprotein. The main metabolite of imatinib, the N-desmethyl derivative CGP74588 (N-desmethylimatinib), is formed in the liver by cytochrome P450 (CYP) 3A4, while a number of other enzymes, including CYP1A2, CYP2D6, CYP2C9 and CYP2C19, are involved in the formation of minor metabolites [19, 20]. CGP74588 accounts for approximately 20% of the plasma drug level

in patients and has similar biological activity to the parent compound but a longer terminal half-life (85–95 h), as measured after discontinuation of therapy [17]. Indeed, Gréen et al. [21] reported that the effect and potency of CGP74588 might have clinical importance.

Imatinib and CGP74588 are mainly glucuronidated to inactive O- and N-glucuronides [16] by UDP-glucuronosyltransferases; however, the UDP-glucuronosyltransferase isoforms involved in the glucuronidation of imatinib have not yet been determined. These glucuronides are excreted into the bile, where they may be converted back to the parent drug and CGP74588 by bacterial β -glucuronidases in the gut lumen. They are then reabsorbed through the process of enterohepatic recirculation, which is evidenced by a secondary plasma peak in the concentration-time profile of imatinib and by the observation that there are conjugates present in the plasma and urine that are not detected in the feces [16]. However, the extent of the biliary excretion of imatinib glucuronic acid conjugates and their metabolites has not yet been reported.

Urinary excretion accounts for 3–5% of the daily imatinib dose [22]. Although organic anion transporters and organic cation transporter (OCT) 2 play an essential role in the renal elimination of imatinib, an in vitro study showed that organic anion transporters 1 and 3 and OCT2 do not transport imatinib, which is consistent with its relatively low renal clearance [23].

Table 1. Correlation of imatinib pharmacokinetics with clinical response

Ref.	Patients n	Imatinib dose mg/day	Imatinib C ₀ ng/ml	Correlation with response
Marin et al. [14]	84	400	900 (400–1,600)	yes (MMR)
Picard et al. [25]	50 18	400 600	1,058 ± 557 1,444 ± 710	yes (CCyR, MMR)
Larson et al. [26]	351	400	979 ± 530	yes (CCyR)
Forrest et al. [27]	78	400	999 (203–2,910)	no (CCyR, MMR)
Widmer et al. [28]	20	400	NA	no (AUCu vs. HR)
Singh et al. [29]	40	400	700 vs. 2,340	yes (clinical response)
Takahashi et al. [30]	254	400	1,011 ± 565	yes (MMR)

NA = Not available; AUCu = free area under the curve; HR = hematological response.

Both imatinib and CGP74588 are transferred to human breast milk [24]. The milk-plasma imatinib ratio after a daily oral administration of a 400-mg dose reaches 0.5 for imatinib and 0.9 for CGP74588. From an average milk intake for an infant of 728–777 ml/day (range 450–1,165 ml/day), the amount of drug transferred to an infant can be calculated to be less than 3 mg/day [24].

The Need for Therapeutic Drug Monitoring

It was recently reported that variation in the imatinib plasma trough concentration (C₀) can affect the clinical response of patients (table 1) [14, 25–30]. Picard et al. [25] reported that a steady-state imatinib C₀ measured after at least 12 months of treatment with a standard imatinib dose correlated with both the cytogenetic and molecular responses. Those investigators suggested that the threshold for the imatinib C₀ should be set above 1,002 ng/ml, as a concentration-effect receiver operating characteristic curve analysis indicated that this level was significantly associated with a MMR with greatest sensitivity (77%) and specificity (71%) [25]. In addition, Larson et al. [26]

reported that a steady-state imatinib C₀ at or above 1,000 ng/ml on day 28 was predictive of a CCyR, while Takahashi et al. [30] found that the MMR was significantly associated with the age of the patients and the imatinib C₀, whereas the CCyR was associated only with the daily dosage. Both Takahashi et al. [30] and Marin et al. [14] reported that patients with an imatinib C₀ of less than 1,002 ng/ml have a significantly lower rate of successfully achieving an improved MMR ($p = 0.012$ and 0.02 , respectively), but not CCyR. Thus, the efficacy of the threshold C₀ of imatinib should be set above 1,002 ng/ml for CML patients.

Patients are more likely to obtain a satisfactory response if an adequate imatinib C₀ is achieved and maintained. Although additional monitoring of CGP74588 may also be useful [31], it is not presently considered. Furthermore, the percent deviation of the observed imatinib C₀ from the standardized trough level appears to be larger if samples are collected outside the 6-hour window between 21 and 27 h after dosing [18]. For that reason, sampling should be carried out within 24 ± 2 h after taking imatinib. According to the European Leukemia Net recommendations [5], the clinical response of CML patients receiving imatinib therapy should be evaluated at 3, 6, 12 and 18 months. If patients do not achieve CCyR or MMR at these time points, the imatinib C₀ should be assayed and BCR-ABL should be analyzed for mutations.

Standard Dose of Imatinib and Trough Levels

Based on the IRIS study, the established standard dose of imatinib is 400 mg/day for patients with chronic-phase CML [3, 32]. A phase I dose escalation study of imatinib from 25 to 1,000 mg/day across 14 dose levels was conducted in 83 patients with chronic-phase CML, but a maximum tolerated dose was not identified [33]. Most patients who are administered a dose of 300 mg/day or greater respond to treatment, and 400 mg/day is recommended as a standard dose, based on clinical and pre-clinical data [12, 33]. Several studies have suggested that administration of a dose higher than 400 mg/day may improve the response in some patients [34] and, in fact, a better response was observed in the accelerated and blast phases of CML with a dose of 600 mg/day [35].

At the recommended dose of 400 mg/day, imatinib sometimes causes severe adverse events, such as myelosuppression, edema and skin rash, which in turn may lead to poor compliance, premature cessation of treatment or failure of the therapy. To avoid these unfavorable clinical

situations, the daily dose of imatinib is often reduced from 400 to 200–300 mg/day in clinical practice [36–40], although maintaining a low dose of imatinib is not generally recommended because of the risk of acquiring BCR-ABL point mutations. Kawaguchi et al. [40] suggested that a dose of 300 mg/day of imatinib might be sufficient to achieve a CCyR or MMR in some Japanese patients, because the significantly smaller body surface area of these patients enables a lower imatinib dose to provide a sufficient C_0 during CML treatment [39, 40]. The mean steady-state imatinib C_0 obtained 24 h after taking a 400-mg daily dose ranged from 900 to 1,400 ng/ml [14, 25–27, 30]; however, even among those taking the same 400 mg/day dose, the imatinib C_0 varied widely (153–3,910 ng/ml) [26]. Kawaguchi et al. [40] reported that the mean C_0 obtained with a dose of 300 mg/day was $1,150 \pm 440$ ng/ml ($n = 9$), exceeding the effective plasma threshold for imatinib C_0 (1,002 ng/ml). Similarly, Sakai et al. [39] reported that the median imatinib C_0 in patients administered 300 mg/day was 1,130 ng/ml, though this result was based on a relatively small number of patients ($n = 13$).

Influence of Comedication on Imatinib Pharmacokinetics

Imatinib absorption is not influenced by food [41]. The concomitant administration of an Mg^{2+} - Al^{3+} -based antacid is not associated with meaningful alterations in imatinib absorption either [41]. Likewise, administration of 40 mg of omeprazole, a proton pump inhibitor, is not associated with a change in the pharmacokinetics of imatinib after a 400-mg dose [42]. Although proton pump inhibitors can influence the absorption and metabolism of drugs by interacting with P-glycoprotein and the CYP enzyme system, no drug interactions between proton pump inhibitors and imatinib via CYP or P-glycoprotein have been observed.

A drug interaction does occur with coadministration of imatinib and rifampicin or St. John's wort, two CYP3A inducers, resulting in a decrease in the plasma concentration of imatinib [43, 44]. In one study, rifampicin significantly reduced the maximum plasma imatinib concentration (C_{max}) by 54% and reduced the dose-adjusted area under the time-concentration curve extending from 0 to 24 h (AUC_{0-24}) by 68%. It also increased the C_{max} and AUC_{0-24} for CGP74588 by 88.6 and 23.9%, respectively [43]. In addition, Smith et al. [44] reported that St. John's wort significantly reduced the C_{max} and $AUC_{0-\infty}$ for imatinib by 29 and 32%, respectively. Similarly, Frye et al. [45]

reported that coadministration of imatinib with St. John's wort significantly reduced the C_{max} and $AUC_{0-\infty}$ of imatinib by 18 and 30%, respectively. Conversely, ketoconazole, a potent CYP3A4 inhibitor, significantly increased the C_{max} and AUC_{0-24} for imatinib by 26 and 40%, respectively, and decreased the C_{max} and AUC_{0-24} for CGP74588 by 22.6 and 13%, respectively [46]. These findings indicate that CGP74588 is produced by CYP3A4 in the small intestine and liver and suggest that, although the clinical effect of St. John's wort or ketoconazole on the response to imatinib appears to be small, one should be alert for this combination. Notably, coadministration of the CYP3A4 inhibitor ritonavir with imatinib for 3 days reportedly produced no apparent drug-drug interaction in patients in the steady state [13]. However, the period examined in that study was too short to draw a meaningful conclusion about a drug-drug interaction between imatinib and ritonavir. Imatinib is also metabolized to a minor extent by CYP1A2; nonetheless, the pharmacokinetics of imatinib are not affected by tobacco smoking, which is known to induce CYP1A1 and CYP1A2 [47, 48].

In the absence of prospective data supporting the maintenance of imatinib C_0 at or above 1,000 ng/ml, escalation of the imatinib dose should be the first choice for a change in therapy for patients with no drug-drug interaction or adherence issues. For CML patients that have an imatinib C_0 of 1,000 ng/ml but lack a sufficient clinical response, switching to another tyrosine kinase inhibitor is recommended.

Factors Influencing Imatinib Exposure

Effect of Liver and Renal Dysfunction

Ramanathan et al. [49] reported that imatinib exposure does not differ between patients with normal liver function and those showing liver dysfunction. Although imatinib is metabolized by hepatic CYP enzymes, their study showed no correlation between imatinib exposure and liver function or the occurrence of dose-limiting toxicities. On the other hand, the hemoglobin concentration was correlated with the clearance of oral imatinib [50].

Pappas et al. [51] reported that the pharmacokinetic parameters for imatinib in a patient on hemodialysis did not differ from those in patients with normal renal function. On the other hand, Gibbons et al. [22] reported that the dose-adjusted C_{max} for imatinib was approximately 2.2-fold higher and the imatinib AUC_{0-24} was significantly greater in patients with mild or moderate renal dysfunction than in those with normal renal function. It

has also been reported that the steady-state imatinib C_0 is significantly associated with creatinine clearance in patients with gastrointestinal stromal tumors [52].

Body Weight

A population pharmacokinetic analysis by Schmidli et al. [50] ($n = 371$) found that body weight was correlated with the clearance of oral imatinib. Kawaguchi et al. [40] reported that in patients ($n = 9$) with a smaller body size, a dose of 300 mg/day is sufficient to obtain therapeutic efficacy equivalent to the standard 400 mg/day dose, as the imatinib C_0 exceeds the therapeutic concentration (1,002 ng/ml). For example, a lower dose of imatinib (200–300 mg/day) provided clinical benefit to 5 Japanese CML patients with a low body surface area (BSA; median value, 1.46 m²) [36], and Korean CML patients with a low BSA (median value, 1.55 m²) benefited similarly from 300 mg/day imatinib [37]. An IRIS subanalysis identified a weak correlation between steady-state imatinib C_0 and both body weight ($r^2 = 0.015$) and BSA ($r^2 = 0.038$; $n = 315$) [26]. On the other hand, no correlation was observed between imatinib C_0 and body weight or BSA in 254 Japanese CML patients [30]. Indeed, given the large interpatient variability in imatinib C_0 (54%), the effects of age, sex and body weight and BSA on imatinib exposure are unlikely to be clinically significant [26].

The Impact of Pharmacogenetic Variation on Imatinib Pharmacokinetics

Pharmacogenetic research on imatinib has focused in part on the relation between imatinib exposure and the clinical response to imatinib (pharmacodynamic effect) and the expression levels of enzymes such as CYP3A4/5 and transporters such as P-glycoprotein, BCRP and OCT1 (pharmacokinetic effects, fig. 1). For example, the level of *SLC22A1* (OCT1) expression likely correlates with the intracellular imatinib concentration, as primary CML cells expressing high levels of OCT1 show greater drug uptake than those exhibiting more modest OCT1 expression [10, 53, 54].

Imatinib exposure may also be influenced by various polymorphisms [55]. In adults, the main CYP3A isoforms are CYP3A4 and CYP3A5, which show approximately 83% amino acid sequence identity [56, 57]. Two polymorphisms, *CYP3A4*1B* (–392A→G) and *CYP3A5*3* (6986A→G), have no significant effect on the plasma concentration of imatinib [58–60], suggesting that *CYP3A4* and *CYP3A5* polymorphisms likely do not have a clinically

Fig. 2. A proposal for a therapeutic strategy for CML patients, based on *ABCG2* polymorphism analysis. If analysis for the *ABCG2* 421C→A genetic polymorphism is possible in the hospital laboratory, the imatinib dosage should be decided on the basis of genotype. To achieve the 1,000 ng/ml C_0 in plasma, the initial daily dosage of imatinib should be 400 mg for patients with the *ABCG2* 421C/C genotype and 300 mg for patients with the 421C/A or 421A/A genotype.

cally significant effect on imatinib exposure. On the other hand, imatinib is a substrate for the ABC efflux transporters ABCB1 and ABCG2 [61–65]. P-glycoprotein, which is encoded by the *ABCB1* gene, is a membrane efflux transporter normally expressed in the small intestine and biliary canicular front of hepatocytes [66]. Three studies have focused on whether *ABCB1* polymorphisms, including 1236C→T, 2677G→T/A and 3435C→T, affect imatinib pharmacokinetics [58–60]. Gurney et al. [59] (sample size = 22) reported that clearance of oral imatinib in patients receiving 600 mg daily was significantly lower in subjects with the *ABCB1* 1236C/C, 2677G/G and 3435C/C genotypes than in those with the corresponding *ABCB1* 1236T/T, 2677T/T and 3435T/T genotypes [59]. However, Gardner et al. [58] (sample size = 82) reported that the *ABCB1* 3435C→T polymorphism had no significant effect on clearance of oral imatinib, and Takahashi et al. [60] (sample size = 62) reported that the 1236C→T, 2677G→T/A and 3435C→T polymorphisms had no significant effect on dose-adjusted imatinib C_0 .

BCRP is encoded by the *ABCG2* gene and is widely expressed in the small intestine, liver and placenta [67, 68]. Takahashi et al. [60] (sample size = 62) reported that the dose-adjusted imatinib C_0 was significantly lower in Japa-

nese patients with the *ABCG2* 421C/C genotype than in patients with the C/A + A/A genotypes. In addition, Petaín et al. [69] (sample size = 46) reported that imatinib clearance in patients carrying the *ABCG2* 421C/A genotype was significantly lower than in those with the 421C/C genotype. It thus appears that among CML patients, the *ABCG2* 421C/A or A/A genotype is associated with a higher imatinib exposure (as C_0) than the 421C/C genotype.

On the other hand, imatinib is also a substrate of the uptake transporter OCT1 [53, 54, 70], which is encoded by *SLC22A1*. OCT1 is primarily expressed on hepatocytes, suggesting that it plays a role in substrate uptake into the liver [71–73]. However, no association between the clearance of oral imatinib and the *SLC22A1* 286C→T or 1498G→A polymorphisms has been observed [23], and Takahashi et al. [60] (sample size = 62) reported that the *SLC22A1* 156T→C, 480G→C, 1022C→T and 1222A→G polymorphisms have no significant effect on dose-adjusted imatinib C_0 . Apparently, the *SLC22A1* polymorphisms analyzed to date have no important effect on imatinib exposure. It may be that although OCT contributes to the cellular uptake of imatinib, it does not contribute to imatinib exposure.

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

most strongly influence imatinib exposure (fig. 1). Takahashi et al. [60] reported that to attain the 1,000 ng/ml drug plasma threshold, the daily dosage of imatinib should be 400 mg in patients with the *ABCG2* 421C/C genotype and 300 mg in those with the 421C/A or 421A/A genotype. Knowledge of the 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 therapeutic drug monitoring could aid patient management (fig. 2).

Conclusions

The interindividual variation of imatinib C_0 is influenced by multiple factors, including genetic polymorphisms, environmental factors, concomitant disease and coadministered drugs. Therefore, a therapeutic drug monitoring service should be routinely provided to CML patients taking imatinib. For CML patients who have an imatinib C_0 of 1,000 ng/ml but lack a sufficient clinical response, switching to another tyrosine kinase inhibitor is recommended. In addition, knowledge of the *ABCG2* 421C→A genotype before initiating therapy could be useful when making dosing decisions aimed at achieving optimal imatinib exposure.

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