Pharmacokinetic Drug Interaction Between Cyclosporine and Imatinib in Bone Marrow Transplant Children and Model-Based Reappraisal of Imatinib Drug Interaction Profile

Nathalie Bleyzac, PharmD, PhD,† Kamila Kebaili, MD,* Valérie Mialou, MD,‡ Yves Bertrand, MD, PhD,* and Sylvain Goutelle, PharmD, PhD†§*

Background: Previous reports have suggested that imatinib may increase cyclosporine exposure by CYP3A4 inhibition. However, the magnitude of this drug interaction remains unclear. At present, quantitative information about the interaction profile of imatinib is scarce.

Methods: The authors report the effect of imatinib on cyclosporine exposure in 6 pediatric patients with Philadelphia chromosome–positive acute lymphoblastic leukemia who received cyclosporine after hematopoietic stem-cell transplantation. Dose-normalized cyclosporine trough blood concentrations (TBC) were obtained before and after imatinib introduction. In addition, a validated model-based approach was used to derive quantitative predictions of CYP3A4-mediated drug interactions with imatinib as a victim or precipitant drug.

Results: The mean dose-normalized cyclosporine TBC significantly increased after 3 to 7 days of imatinib therapy. The modeling approach predicted weak-to-moderate effect of major CYP3A4 inhibitors on imatinib exposure. However, the inhibitory potency of imatinib was found to be similar to that of verapamil, suggesting significant influence of imatinib on the pharmacokinetics of drugs highly metabolized by CYP3A4. Observed increases in cyclosporine dose-normalized TBC of the 6 patients were compatible with model predictions. The observations and predictions suggest that imatinib may substantially increase cyclosporine exposure.

Conclusions: Cyclosporine dose reduction may be necessary to avoid excessive immunosuppressive effect in case of coadministration of imatinib.

Key Words: cyclosporine, imatinib, drug interaction, children, bone marrow transplantation

(*Ther Drug Monit* 2014;36:724–729)

Received for publication October 7, 2013; accepted April 8, 2014.

From the *Institut d'Hématologie et d'Oncologie Pédiatrique, Hospices Civils de Lyon; †Laboratoire de Biométrie et Biologie Evolutive, Université Lyon 1, Villeurbanne; ‡Etablissement Français du Sang Rhône-Alpes, Banque des cellules et Tissus, Hôpital Edouard Herriot, Lyon; and §Université Lyon 1, Institut des Sciences Pharmaceutiques et Biologiques—Faculté de Pharmacie de Lyon, France.

The authors declare no conflict of interest.

Correspondence: Nathalie Bleyzac, PharmD, PhD, Institut d'Hématologie et d'Oncologie Pédiatrique, 1 place Joseph Renaut, 69008 Lyon, France (e-mail: nathalie.bleyzac@chu-lyon.fr).

INTRODUCTION

Imatinib has become the standard therapy for chronic myeloid leukemia. In addition, it has been successfully introduced in chemotherapy regimens for Philadelphia chromosome–positive (Ph^+) acute lymphoblastic leukemia (ALL).[1,2] Despite this progress, hematopoietic stem-cell transplantation (HSCT) is still required in patients with high-risk ALL. Until recent years, long-term survival rates after myeloablative HSCT in Ph^+ ALL did not exceed 40% to 45% in adults and children, and relapse was the most frequent cause of failure.[3,4] Minimal residual disease was frequently observed in patients after HSCT for Ph^+ ALL and was associated with an increased risk of relapse.[3,5,6] It has been shown that imatinib can reduce post-transplant minimal residual disease, and therefore prevent recurrent ALL after HSCT, with an increase in overall survival up to 60%.[7,8]

Imatinib is metabolized in the liver by cytochromes P450 3A4 (CYP3A4) and 2C8.[9] Imatinib and its *N*-desmethyl metabolite are also moderate competitive inhibitors of CYP2C8 and CYP3A4/5. Imatinib may also inhibit CYP3A4 through a potent irreversible mechanism.[10] Also, it has been shown that imatinib is both a substrate and a modulator of P-glycoprotein (P-gp).[11] As a result, imatinib may be involved in a number of drug–drug interactions, as a victim or precipitant drug.[12] Although interactions between imatinib and cytochrome P450 or P-gp inhibitors have been well documented,[13,14] little is known about the influence of imatinib on the exposure to other drugs, except for simvastatin.[15]

Cyclosporine A (CsA) is an immunosuppressant agent that is still widely used in HSCT recipients, and it may be administered in combination with imatinib in transplanted Ph^+ ALL patients. Similar to imatinib, cyclosporine is a substrate of both CYP3A4 and P-gp, and it is also a CYP3A4 and P-gp inhibitor.[16] As a result, a reciprocal interaction is expected between imatinib and CsA: on the one hand inhibition of CYP3A4 and P-gp by CsA may increase imatinib exposure; on the other hand, imatinib may also increase the exposure to CsA through the same mechanisms.[12] However, little is known about the clinical implications of such an interaction between imatinib and cyclosporine, and no data are available for children.

We report a case series suggesting a substantial effect of imatinib on CsA blood levels in young patients with Ph^+ ALL

after HSCT. In addition, we reassess the effect of induction and inhibition of CYP3A4 on imatinib exposure, as well as the inhibition of CYP3A4 caused by imatinib using a validated modeling approach and published data.

PATIENTS AND METHODS

Patients

Six patients aged 8 to 19 years underwent allogeneic stem-cell transplantation for Ph^+ ALL in first (n = 4) or second complete remission (n = 1) and Ph^+ lymphoblastic lymphoma (n = 1) in the Paediatric Haematology and Oncology Institute of Lyon, France, between 2003 and 2012. Children received matched (n = 3) or mismatched (n = 3) unrelated donor grafts after conditioning with total-body irradiation, etoposide (60 mg/kg), and rabbit antithymocyte globulins (7.5 mg/kg) combined with CsA for graft-versus-host disease (GVHD) prophylaxis.

Trough blood concentrations (TBC) of CsA were measured twice weekly during the first month after transplantation, and then once weekly by antibody-conjugated magnetic immunoassay. CsA dosing regimens were individually adjusted using a Bayesian approach as described elsewhere.[17] CsA trough blood levels at the steady-state were available for all patients before imatinib was started. Imatinib was introduced between day 40 and day 74 after transplantation, at a dose of 280 $mg \cdot m^{-2} \cdot d^{-1}$. At the time of imatinib starting, all but 1 patient received CsA orally. Other concomitant drugs were acyclovir, phenoxymethylpenicillin, and cotrimoxazole used for the prevention of infectious diseases. Dosage regimens of these drugs were constant, and no other drug was added during the studied period. CsA TBC were measured in all patients within the first week (between day 3 and day 7) after imatinib onset. In 5 of 6 patients, a second measurement of CsA trough concentration was performed during the second week after imatinib introduction (between day 8 and day 15). Imatinib was stopped after the third week of treatment in 3 patients because of poor response, and CsA TBC were measured within the week after imatinib withdrawal in those patients.

Slight dose adjustments were performed to control CsA blood concentration at the individual target for each patient over the study period. Target TBC was set at 120 ng/mL in patients without GVHD and 150 to 200 ng/mL in case of GVHD occurrence, depending on the GVHD severity.[17] Because of those individual changes in CsA dose over the study period, we did not examine the actual CsA trough concentrations but dose-normalized trough concentrations, expressed as the ratios of CsA TBC (in units of microgram of CsA per liter) over CsA daily dose (in milligram of CsA per kilogram of body weight). Daily doses were expressed per kilogram of actual body weight, which may also have changed a little over the study period in some patients. Although the unit of dose-normalized TBC is (mcg × kg)/(L × mg), the respective results are reported without unit throughout the article for ease of reading. Dose-normalized TBC were compared before and after introduction of imatinib using the Wilcoxon signed-rank test for matched samples, with statistical significance set at a P value of 5%.

The possible role of the drugs coadministered in the alteration of drug exposure was examined for each patient using the Horn drug interaction probability scale.[18]

Prediction of Drug Interactions With Imatinib

We assessed the potency of imatinib to inhibit CYP3A4 using a quantitative approach described in detail elsewhere.[19–22] Briefly, it may be shown that the alteration in the AUC of a substrate drug of CYP3A4 caused by an inhibitor of this cytochrome can be described by the following equation:

$$\frac{AUC^*}{AUC} = \frac{1}{1 - CR_{CYP3A4} * IR_{CYP3A4}} \quad (1)$$

where AUC is the reference AUC of the drug when administered alone, AUC* is the AUC of the drug when coadministered with a CYP3A4 inhibitor, CR_{CYP3A4} is the contribution ratio of the substrate drug (ie, the fraction of the apparent oral drug clearance due to CYP3A4, ranging from 0 to 1), IR_{CYP3A4} is the inhibition ratio, a measure of the inhibitor potency. The inhibition ratio ranges from 0 (the inhibitor has no effect on CYP3A4-mediated clearance of the victim drug) to 1 (the inhibitor reduces CYP3A4-mediated clearance of the victim drug to zero). As a result, for a substrate drug metabolized by CYP3A4, the increase in the drug exposure caused by an inhibitor and quantified by the AUC ratio (AUC*/AUC) is a function of the inhibitor potency (IR_{CYP3A4}) and the relative contribution of the CYP3A4 pathway in the metabolism of the victim drug (CR_{CYP3A4}). Of note, this equation only applies for drug–drug interactions occurring in extensive metabolizers for a given cytochrome, and for substrate drugs administered by the oral route, with linear pharmacokinetics.[19,21] This equation has been successfully applied to quantify drug–drug interactions for a number of drugs metabolized by CYP3A4,[19,20] CY2D6,[21] CYP2C9,[23] and CYP2C19.[22]

In case of CYP3A4 induction, the equation describing the alteration in substrate drug exposure is as follows[20]:

$$\frac{AUC^*}{AUC} = \frac{1}{1 + CR_{CYP3A4} * IC_{CYP3A4}} \quad (2)$$

where IC_{CYP3A4} represents the apparent increase in the clearance of substrates produced by induction of CYP3A4. This parameter is a real positive number and quantifies the inducer potency.

We used equations 1 and 2, as well as published data from several drug interaction studies to estimate the CR_{CYP3A4} of imatinib as a CYP3A4 substrate and its IR_{CYP3A4} as a CYP3A4 inhibitor. First, results from a drug interaction study of imatinib and rifampicin were used to obtain an initial estimate of imatinib CR_{CYP3A4}.[24] The AUC ratio of imatinib (AUC*/AUC) found in this study and the IC_{CYP3A4} of rifampicin (7.7)[20] were used to derive imatinib CR_{CYP3A4} using Equation 2. Then, an initial estimate of IR_{CYP3A4} of imatinib was calculated using data from a study that assessed the inhibitory effect of imatinib on the pharmacokinetics of simvastatin.[15] The AUC ratio of simvastatin (AUC*/AUC) found in this study, as well the simvastatin CR_{CYP3A4} value of 1 reported by Ohno et al[19] were used to derive IR_{CYP3A4} using Equation 1.

Then, Bayesian orthogonal regression was performed in the WinBUGS software, version 1.4.3[25] to derive final estimates of CR_{CYP3A4} and IR_{CYP3A4} for imatinib, as well as AUC ratios for a number of drug–drug interactions with imatinib as the victim drug (effect of known CYP3A4 inhibitors on imatinib exposure) or the precipitant drug (inhibitory effect of imatinib on CYP3A4 substrate drugs). Orthogonal regression is a standard linear regression technique that may be used when the independent variables (predictors) are known with errors, which was the case of published AUC ratios.[26,27] This Bayesian approach has been described in detail elsewhere.[21,22] The full database used in the Bayesian analysis included published drug interaction data for 27 CYP3A4 substrate drugs and 18 CYP3A4 inhibitors. This article reports the quantitative predictions of drug–drug interactions calculated for imatinib only. Two Markov chains were used in the Bayesian estimation. A total of 80,000 iterations were performed to estimate the Bayesian posterior distributions of the parameters. Convergence was checked by visual inspection of the trace plots of the parameters and stability of the posterior distributions. The Monte Carlo error provided by WinBUGS was used to assess the accuracy of posterior estimates. Goodness-of-fit was assessed by visual examination of the residual scatter plots and the shape of posterior distributions (a unimodal distribution was expected and eventually observed for all parameters).

RESULTS

Patients

CsA daily doses and TBC over the study period are reported in Table 1. The mean dose-normalized TBC significantly increased from 33.5 ± 12.8 (range, 17.9–51.2) to 58.8 ± 23.6 (range, 28.2–100.8) after 3 to 7 days of imatinib therapy ($P = 0.028$). The mean percent increase in CsA dose-normalized TBC was 78.3% ± 39.1% (range, 17.7%–129.7%). Intraindividual variability in dose-normalized TBC observed in the 6 patients over the 3 weeks before introduction of imatinib was much lower (4.7 ± 2.6, estimated on 5.3 ± 0.8 occasions per patient) than the alteration observed after imatinib introduction.

In the second week of concomitant administration of imatinib (days 8–14), the mean dose-normalized TBC was slightly increased compared with that of the first week (62.8 ± 31.8), although this value decreased in 2 subjects. During coadministration with imatinib, CsA dose reductions ranging from −48% to −78% were necessary to maintain CsA TBC to levels similar to those observed before imatinib introduction.

In the 3 patients in whom imatinib was stopped because of poor tolerance (headache or edemia), a large decrease in CsA TBC was observed (TBC were measured between 3 and 7 days after imatinib discontinuation). Dose-normalized TBC decreased from 38.7 to 23.1 in patient 3, from 83.9 to 26.5 in patient 4, and from 55.6 to 33.3 in patient 6.

The Horn drug interaction probability scale[18] indicated a probable interaction (total score = 6) between CsA and imatinib, whereas the interaction with other coadministered drugs was found as doubtful (total score <2) for each case.

Prediction of Drug Interactions With Imatinib

A summary of drug interaction studies with imatinib performed in humans is presented in Table 2. Bolton et al[24] reported a significant decrease in imatinib exposure (AUC*/AUC = 0.26) caused by rifampicin (600 mg/d over 7 days), a known CYP34A inducer with an IC_{CYP3A4} of 7.7.[20] Using these data in Equation 2, an initial CR_{CYP3A4} estimate of 0.37 was calculated for imatinib. Using the 3.5-fold mean increase in simvastatin AUC observed after 7 days of coadministration with imatinib (400 mg daily) reported by O'Brien et al,[15] and a CR_{CYP3A4} of 1.0 estimated by Ohno et al for simvastatin, we estimated an initial estimate of imatinib IR_{CYP3A4} of 0.71 using Equation 1.

Bayesian orthogonal regression analysis provided final estimates of CR_{CYP3A4} and IR_{CYP3A4} for imatinib of 0.35 [95% confidence interval (CI), 0.17–0.54] and 0.70 (95% CI, 0.59–0.79), respectively, which were very close to initial estimates.

The predicted AUC ratio of imatinib when coadministered with 17 CYP3A4 inhibitors are shown in Figure 1. Our model-based approach predicted limited effect of strong CYP3A4 inhibitors such as triazole antifungal agents, ritonavir, or clarithromycin on imatinib exposure, with a maximum AUC increase about 1.5-fold. Figure 2 shows the predicted

TABLE 1. Variations in CsA TBC Associated With Imatinib Treatment

Patient	CsA Dose and TBC Before Imatinib Onset	CsA Dose and TBC After 3–7 Days of Imatinib Therapy	CsA Dose and TBC After 8–14 Days of Imatinib Therapy	Adjusted CsA Dose and TBC During Imatinib Therapy
1	3.9 mg·kg^{-1}·d^{-1} (PO), 200 ng/mL	4.0 mg·kg^{-1}·d^{-1} (PO), 403 ng/mL	3.5 mg·kg^{-1}·d^{-1} (PO), 396 ng/mL	2.3 mg·kg^{-1}·d^{-1} (PO), 200 ng/mL
2	3.2 mg·kg^{-1}·d^{-1} (PO), 150 ng/mL	2.9 mg·kg^{-1}·d^{-1} (PO), 160 ng/mL	2.5 mg·kg^{-1}·d^{-1} (PO), 180 ng/mL	2.1 mg·kg^{-1}·d^{-1} (PO), 130 ng/mL
3	3.8 mg·kg^{-1}·d^{-1} (PO), 100 ng/mL	4.8 mg·kg^{-1}·d^{-1} (PO), 290 ng/mL	3.8 mg·kg^{-1}·d^{-1} (PO), 150 ng/mL	3.1 mg·kg^{-1}·d^{-1} (PO), 120 ng/mL
4	3.7 mg·kg^{-1}·d^{-1} (IV), 110 ng/mL	4.6 mg·kg^{-1}·d^{-1} (IV), 230 ng/mL	not documented	not documented
5	7.8 mg·kg^{-1}·d^{-1} (PO), 140 ng/mL	7.8 mg·kg^{-1}·d^{-1} (PO), 220 ng/mL	7.7 mg·kg^{-1}·d^{-1} (PO), 260 ng/mL	4.8 mg·kg^{-1}·d^{-1} (PO), 150 ng/mL
6	4.8 mg·kg^{-1}·d^{-1} (PO), 140 ng/mL	4.8 mg·kg^{-1}·d^{-1} (PO), 280 ng/mL	4.3 mg·kg^{-1}·d^{-1} (PO), 240 ng/mL	2.5 mg·kg^{-1}·d^{-1} (PO), 150 ng/mL

TABLE 2. Summary of Human Drug Interaction Studies With Imatinib

Victim Drug	Precipitant Drug Daily Dose	Study Design	Mechanism	AUC*/AUC of Victim Drug	Reference
Imatinib	Rifampicin 600 mg	Multiple dose	Induction	0.26	24
Imatinib	St John's wort 900 mg	Multiple dose	Induction	0.70	26
Imatinib	Ketoconazole 400 mg	Single dose	Inhibition	1.38	13
Simvastatin	Imatinib 400 mg	Multiple dose	Inhibition	3.5	15
Cyclosporine	Imatinib 200 mg	Single dose	Inhibition	1.23	27

AUC ratios for 26 CYP3A4 substrates when coadministered with imatinib at a daily dose of 400 mg. With an estimated IR_{CYP3A4} of 0.70, the inhibitor potency of imatinib is similar to that of verapamil.[19] Weak-to-moderate increases in drug exposure are expected for most agents, but coadministration with imatinib may result in significant overexposure (predicted AUC*/AUC greater than 3) for drugs that are highly metabolized by CYP3A4 such as simvastatin, dronedarone, or triazolam.

DISCUSSION

Because both CsA and imatinib are substrate and inhibitor drugs of CYP3A4 and P-gp, a reciprocal interaction has been expected between those 2 drugs.[28] However, little is known about the magnitude of this interaction, especially on the inhibitor potency of imatinib. In a single dose study in healthy volunteers who were administered 200 mg of oral imatinib in combination with 175 mg of CsA, Peng et al[28] observed relatively small variations in exposure of both drugs: the AUC_{0-inf} of imatinib was increased by 10%, and that of CsA was increased by 23%. However, as pointed out by the authors, imatinib was used at a subtherapeutic dose, and so the effect of imatinib on cyclosporine exposure may be greater at therapeutic steady-state concentrations of imatinib. The authors recommended performing therapeutic drug monitoring to adjust CsA dose in case of coadministration with imatinib.

Since this abstract was published, very few data have been reported on CsA dosing during imatinib treatment. Yamada et al[29] reported an increase in the CsA levels in 2 adults after allogeneic HSCT. However, there were 2 limitations in this study: CsA concentrations were assayed in serum instead of blood, and these observations were made during switch from intravenous to oral CsA, which is known to be an important source of pharmacokinetic variability. Also, the interaction was suggested in a renal transplant patient who presented CsA-related renal toxicity during concomitant administration with imatinib treatment.[30] Carpenter et al[31] observed that imatinib did not affect calcineurin inhibitor levels in transplanted patients, but they pooled CsA blood concentrations without taking into account individual variations,

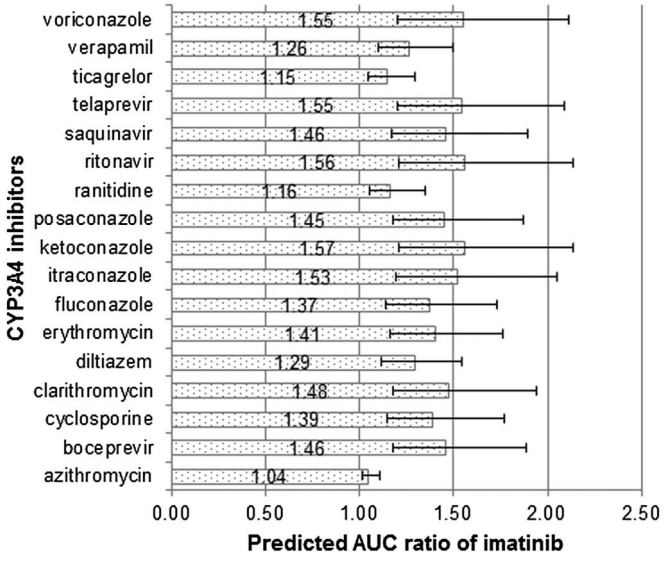

FIGURE 1. Predicted change in imatinib exposure (AUC*/AUC) caused by drug interactions with various CYP3A4 inhibitors. The bars are the mean point estimates of the AUC ratios, and the black lines are the 95 percent CIs of the AUC ratios.

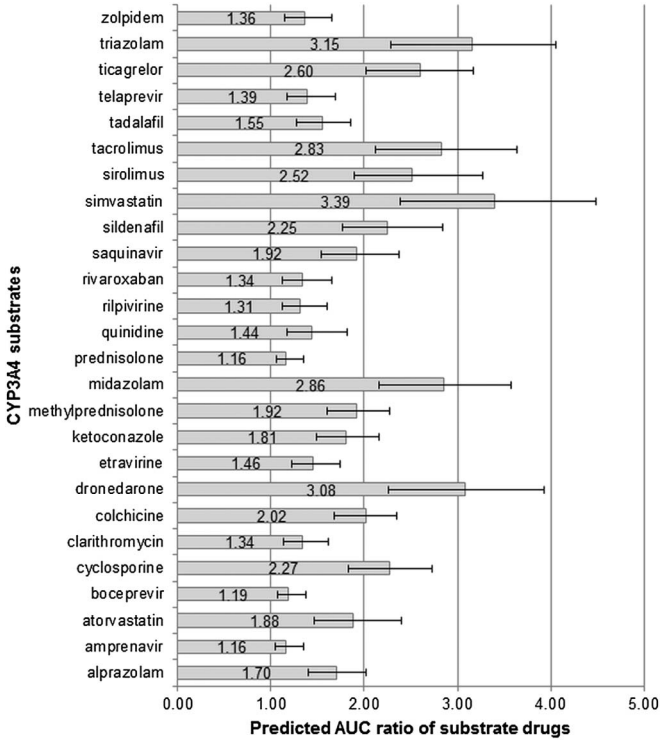

FIGURE 2. Predicted change in drug exposure for various CYP3A4 substrates due to CYP3A4 inhibition by imatinib. The gray bars are the mean point estimates of the AUC ratios, and the black lines are the 95% CIs of the AUC ratios.

intraindividual variability, and amounts administered. To the best of our knowledge, our report covers the largest series of cases supporting a clinically relevant interaction between imatinib and CsA, and our observations are also the first to be reported in children. In this series, we observed a statistically significant increase in dose-normalized CsA TBC associated with the introduction of imatinib, with a mean increase of 78% (range, 57%–130%) after 1 week of imatinib therapy.

To the best of our knowledge, quantitative data on the inhibitory effect of imatinib are only available for 2 drugs: cyclosporine[28] and simvastatin.[15] We used this drug interaction between imatinib and simvastatin as a reference to calculate the initial estimate of imatinib IR_{CYP3A4}. It is noteworthy that simvastatin exposure depends not only on CYP3A4 but also on the hepatic uptake transporter OATP1B1.[32] However, it has been shown that imatinib does not inhibit OATP1B1.[33] Thus, the increase in simvastatin exposure when coadministered with imatinib can be attributed to CYP3A4 inhibition only.

Methods for quantitative prediction of CYP-mediated drug–drug interactions based on in vivo data have been proposed and applied for a large number of CYP substrates and inhibitors.[19,21,22] We used this approach to predict the effect of CYP3A4 inhibitors on imatinib exposure, as well as the effect of imatinib on the exposure to various CYP3A4 substrate drugs. This modeling approach is quite simple because only 2 parameters are necessary to predict the magnitude of a drug–drug interaction: the contribution ratio of the substrate drug (CR_{CYP3A4}) and the inhibition ratio of the inhibitor (IR_{CYP3A4}) in case of a drug interaction by CYP inhibition.

Compared with the results reported by Peng et al[28] (AUC*/AUC = 1.23), the model seems to overestimate the effect of imatinib on CsA exposure (predicted AUC*/AUC = 2.27). However, as explained above, CsA was coadministered with a subtherapeutic single dose of imatinib in the study from Peng et al.[19] Because the inhibitor potency is considered to be dose-dependent, the use of imatinib at a higher dose and at the steady-state should result in greater CYP3A4 inhibition. In our case series, 1.78-fold and 1.81 mean increases in CsA dose-normalized TBC were observed after 1 week and 2 weeks of imatinib therapy, respectively. Those results seem to be fairly compatible with model predictions. However, because CsA trough concentration does not correlate well with CsA AUC, richer data and observed cyclosporine AUC would be necessary to fully confirm the model predictions.

Our observations suggest a substantial effect of imatinib on CsA blood concentrations, but this effect was variable among patients. Factors explaining the interindividual susceptibility to imatinib drug interactions remain to be determined.

Obviously, available in vivo data on drug interactions with imatinib were not sufficient to perform a formal validation of the predictions presented in this article. One may note that the predicted increase in imatinib exposure due to inhibition by ketoconazole (1.57; 95% CI, 1.21–2.02) agrees well with the observed ratio of 1.38 reported by Dutreix et al.[13] In addition, this approach has already been applied and validated for many drugs metabolized by CYP3A4, CYP2D6, CYP2C9, and CYP2C19, providing very good average predictive performance.[19–23]

It is acknowledged that this approach is based on a number of assumptions and has several limitations that have been discussed in detail elsewhere.[19,21] Of note, intestinal metabolism has to be considered in addition to liver metabolism, and it is assumed that drug interactions alter both mechanisms in the same proportion.[19] Also, only drug interactions mediated by CYP are considered in this approach. Other mechanisms such as drug transporters are not taken into account. These simplifications may alter the accuracy of model-based predictions for drugs that are substrates of hepatic and intestinal CYP3A4, as well as substrate of P-gp, such as CsA. One should also note that this approach only provides an average prediction of the alteration in CYP substrate drug exposure, and therefore the clinical alteration may vary between individuals. As a result, model-based predictions of drug interactions with imatinib presented in this study should only be considered as estimates, with a guidance value. However, we believe that these predictions, which are based on all the available prior knowledge about in vivo CYP3A4-mediated drug interactions,[19,20] are the most acceptable quantitative estimates to date.

With an estimated IR_{CYP3A4} of 0.70, the inhibition potency of imatinib seems to be similar to that of verapamil.[19] This suggests that imatinib may substantially alter the pharmacokinetics and pharmacodynamics of widely prescribed drugs including statins and benzodiazepines. Regarding the interaction between CsA and imatinib, although the inhibitory effect of imatinib on CsA exposure is moderate, this interaction may have serious consequences because of the narrow therapeutic index of CsA.

CONCLUSIONS

In HSCT patients, it is desirable to maintain post-transplant immunosuppression at the lowest possible level to allow graft-versus-leukemia effect and lymphocyte subset reconstitution. Recent data also suggest that a pharmacodynamics interaction may occur between CsA and imatinib and modulate drug effect.[34] In case of coadministration of imatinib, the CsA dose may be decreased to avoid excessive immunosuppressive effect. Our data suggest that a 40% preemptive reduction in CsA dose may be performed before imatinib introduction, but the magnitude of this dose reduction has to be confirmed on a larger cohort. Individual dose adjustment of CsA should be guided by therapeutic drug monitoring in any case with TBC to be measured within the first week after imatinib introduction.

Acknowledgments

The authors thank Ms Constance Loue and Professor Michel Tod for providing the database used to perform the Bayesian estimation of imatinib drug–drug interactions.

REFERENCES

1. Wassmann B, Pfeifer H, Goekbuget N, et al. Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph^+ ALL). *Blood*. 2006;108:1469–1477.

2. Yanada M, Takeuchi J, Sugiura I, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. *J Clin Oncol.* 2006;24:460–466.
3. Fielding A, Rowe J, Richards S, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. *Blood.* 2009;113:4489–4496.
4. Arico M, Schrappe M, Hunger SP, et al. Clinical outcome of children with newly diagnosed Philidelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. *J Clin Oncol.* 2010;28: 4755–4761.
5. Schrappe M, Aricò M, Harbott J, et al. Philadelphia chromosome-positive (Ph+) childhood acute lymphoblastic leukemia: good initial steroid response allows early prediction of a favorable treatment outcome. *Blood.* 1998;92:2730–2741.
6. Stirewalt DL, Guthrie KA, Beppu L, et al. Predictors of relapse and overall survival in Philadelphia chromosome-positive acute lymphoblastic leukemia after transplantation. *Biol Blood Marrow Transpl.* 2003;9: 206–212.
7. Burke MJ, Trotz B, Luo X, et al. Allo-hematopoietic cell transplantation for Ph chromosome-positive ALL: impact of imatinib on relapse and survival. *Bone Marrow Transplant.* 2009;43:107–113.
8. Nishiwaki S, Miyamura K, Kato C, et al. Impact of post-transplant imatinib administration on Philadelphia chromosome-positive acute lymphoblastic leukaemia. *Anticancer Res.* 2010;30:2415–2418.
9. Filppula AM, Neuvonen M, Laitila J, et al. Autoinhibition of CYP3A4 Leads to major role of CYP2C8 in imatinib Metabolism: variability in CYP2C8 activity may alter plasma concentrations and response. *Drug Metab Dispos*. 2013;41:50–59.
10. Filppula AM, Laitila J, Neuvonen PJ, et al. Potent mechanism-based inhibition of CYP3A4 by imatinib explains its liability to interact with CYP3A4 substrates. *Br J Pharmacol.* 2012;165:2787–2798.
11. Hamada A, Miyano H, Watanabe H, et al. Interaction of imatinib mesilate with human P-glycoprotein. *J Pharmacol Exp Ther.* 2003; 307:824–828.
12. Haouala A, Widmer N, Duchosal MA, et al. Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib. *Blood*. 2011; 117:e75–87.
13. Dutreix C, Peng B, Mehring G, et al. Pharmacokinetic interaction between ketoconazole and imatinib mesylate (Glivec) in healthy subjects. *Cancer Chemother Pharmacol.* 2004;54:290–294.
14. van Erp NP, Gelderblom H, Karlsson MO, et al. Influence of CYP3A4 inhibition on the steady-state pharmacokinetics of imatinib. *Clin Cancer Res.* 2007;13:7394–7400.
15. O'Brien SG, Meinhardt P, Bond E, et al. Effects of imatinib mesylate (STI571, Glivec) on the pharmacokinetics of simvastatin, a cytochrome P450 3A4 substrate, in patients with chronic myeloid leukaemia. *Br J Cancer.* 2003;89:1855–1859.
16. NEORAL RCP novartis 2009, Food and drug administration. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050715s027. 050716s028lbl.pdf. Accessed February 2013.
17. Bleyzac N. The use of pharmacokinetic models in paediatric oncohaematology: effects on clinical outcome through the examples of busulfan and cyclosporine. *Fundam Clin Pharmacol.* 2008;22:605–608.
18. Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. *Ann Pharmacother.* 2007;41:674–680.
19. Ohno Y, Hisaka A, Suzuki H. General framework for the quantitative prediction of CYP3A4-mediated oral drug interactions based on the AUC increase by coadministration of standard drugs. *Clin Pharmacokinet.* 2007;46:681–696.
20. Ohno Y, Hisaka A, Ueno M, et al. General framework for the prediction of oral drug interactions caused by CYP3A4 induction from in vivo information. *Clin Pharmacokinet.* 2008;47:669–680.
21. Tod M, Goutelle S, Clavel-Grabit F, et al. Quantitative prediction of cytochrome P450 (CYP) 2D6-mediated drug interactions. *Clin Pharmacokinet.* 2011;50:519–530.
22. Goutelle S, Bourguignon L, Bleyzac N, et al. In vivo quantitative prediction of the effect of gene polymorphisms and drug interactions on drug exposure for CYP2C19 substrates. *AAPS J.* 2013;15:415–426.
23. Castellan AC, Tod M, Gueyffier F, et al. Quantitative prediction of the impact of drug interactions and genetic polymorphisms on cytochrome P450 2C9 substrate exposure. *Clin Pharmacokinet.* 2013;52:199–209.
24. Bolton AE, Peng B, Hubert M, et al. Effect of rifampicin on the pharmacokinetics of imatinib mesylate (Gleevec, STI571) in healthy subjects. *Cancer Chemother Pharmacol.* 2004;53:102–106.
25. Spiegelhalter D, Thomas A, Best N, et al. *Winbugs 1.4.3 User Manual*. Cambridge, United Kingdom: MRC Biostatistics Unit IoPH; 2007.
26. Carroll RJ, Ruppert D. The use and misuse of orthogonal regression in linear errors-in-variables models. *Am Stat.* 1996;50:1–6.
27. Tod M, Aouimer A, Petitjean O. Estimation of pharmacokinetic parameters by orthogonal regression: comparison of four algorithms. *Comput Methods Programs Biomed.* 2002;67:13–26.
28. Peng B, Knight H, Riviere GJ, et al. Pharmacokinetic interaction between Gleevec (imatinib) and cyclosporine. *Blood.* 2002;100(suppl):433b–434b.
29. Yamada M, Miyamura K, Fujiwara T, et al. Imatinib mesylate in conjunction with allogeneic hematopoietic stem cell transplantation in patients with Philadelphia chromosome positive leukemias: report of 4 cases. *Tohoku J Exp Med.* 2004;204:79–84.
30. Mulder KE, Egorin MJ, Sawyer MB. Renal dysfunction in a renal transplant patient treated concurrently with cyclosporine and imatinib. *Invest New Drugs*. 2012;30:2400–2402.
31. Carpenter PA, Snyder DS, Flowers MED, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. *Blood*. 2007;109:2791–2793.
32. Elsby R, Hilgendorf C, Fenner K. Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. *Clin Pharmacol Ther.* 2012;92:584–598.
33. Bergman E, Hedeland M, Bondesson U, et al. The effect of acute administration of rifampicin and imatinib on the enterohepatic transport of rosuvastatin in vivo. *Xenobiotica.* 2010;40:558–568.
34. Blake SJ, Hughes TP, Lyons AB. Drug-interaction studies evaluating T-cell proliferation reveal distinct activity of dasatinib and imatinib in combination with cyclosporine A. *Exp Hematol.* 2012;40:612–621.e6.