

A Long-term Prospective Population Pharmacokinetic Study on Imatinib Plasma Concentrations in GIST Patients

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Abstract

Purpose: Imatinib minimal (trough) plasma concentrations after one month of treatment have shown a significant association with clinical benefit in patients with gastrointestinal stromal tumors (GIST). Considering that a retrospective pharmacokinetic analysis has also suggested that imatinib clearance increases over time in patients with soft tissue sarcoma and GIST, the primary aim of this study was to assess systemic exposure to imatinib at multiple time points in a long-term prospective population pharmacokinetic study. As imatinib is mainly metabolized in the liver, our secondary aim was to elucidate the potential effects of the volume of liver metastases on exposure to imatinib.

Experimental Design: Full pharmacokinetic blood sampling was conducted in 50 patients with GIST on the first day of imatinib treatment, and after one, six, and 12 months. In addition, on day 14, and monthly during imatinib treatment, trough samples were taken. Pharmacokinetic analysis was conducted using a compartmental model. Volume of liver metastases was assessed by computed tomographic (CT) imaging.

Results: After 90 days of treatment, a significant decrease in imatinib systemic exposure of 29.3% compared with baseline was observed ($P < 0.01$). For every 100 cm³ increase of metastatic volume, a predicted decrease of 3.8% in imatinib clearance was observed.

Conclusions: This is the first prospective pharmacokinetic study in patients with GIST, showing a significant decrease of approximately 30% in imatinib exposure after long-term treatment. This means that future "trough level – clinical benefit" analyses should be time point specific. GIST liver involvement, however, has a marginal effect on imatinib clearance. *Clin Cancer Res*; 18(20); 5780–7. ©2012 AACR.

Introduction

After a decade of therapeutic use, imatinib mesylate has proven to be a highly effective targeted agent in the treatment of patients with advanced gastrointestinal stromal tumor (GIST), with a median overall survival close to 5 years (1). Imatinib mesylate is a small molecule that inhibits intracellular autophosphorylation of 2 tyrosine kinase receptors involved in the pathogenesis of GIST: mainly KIT and to a lesser extent platelet-derived growth factor receptor- α (PDGFR- α ; refs. 2, 3). Although a vast majority of

patients with GIST will show clinical benefit from imatinib therapy, approximately 10% to 15% will experience progressive disease within 3 to 6 months after the start of treatment (4–6). Mechanisms behind this so-called early progression are not entirely elucidated. Although a majority of nonresponding patients harbor mutations in the molecular drug targets (3, 7, 8), early resistance may also result from imatinib plasma levels that are below a minimal effective threshold level. Although not significant, patients with GIST not responding to imatinib treatment have shown lower imatinib plasma levels than responders (9, 10). In addition, in a retrospective pharmacokinetic side-study of the pivotal phase II B2222 trial, a significant shorter time to progression was observed in patients that showed one-month imatinib steady-state trough levels below 1,100 ng/mL (10). Considering a retrospective pharmacokinetic analysis has also suggested that imatinib clearance increases over time in patients with soft tissue sarcoma and GIST, the primary aim of this study was to assess systemic exposure to imatinib at multiple time points in a long-term prospective population pharmacokinetic study (11).

Imatinib is extensively metabolized and cleared by the liver with 68% of the dose recovered in faeces (12). Its main metabolite CGP74588 is formed by hepatic oxidases from the cytochrome P450 superfamily (CYP) with isoforms 3A4

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Translational Relevance

Although imatinib treatment has proven efficacy in gastrointestinal stromal tumors (GIST), ultimately, progression of disease occurs due to drug resistance. Several mechanisms of drug resistance exist, with the putative role of "pharmacokinetic resistance" still largely unexplored. Efflux transporters (i.e., the ATP-binding cassette transporters ABCB1 and ABCG2) and influx transporters (i.e., the organic cation transporters OCT1 and the organic anion transporting peptide OATP1A2) may play an important role in this type of resistance. An altered expression of these transporters may lead to an increased clearance of the drug and lowered plasma concentrations of imatinib over time. In this article, long-term pharmacokinetics in patients with GIST are studied prospectively to elucidate its role in pharmacokinetic resistance, leading to implications for future studies and treatment with imatinib.

and 3A5 (CYP3A4 and CYP3A5, respectively) as its predominant members (13). As a secondary objective, we therefore studied the potential metabolic effects of liver metastatic involvement on the exposure to imatinib.

Materials and Methods

Patients

Patients with histologically confirmed GIST were accrued at start of imatinib therapy for long-term imatinib pharmacokinetic assessment in 2 Dutch and 2 Italian medical centers. Patients treated with drugs known to show major interactions with cytochrome P450 isoforms, 3A4 and 3A5 (CYP3A4 and CYP3A5), were excluded from the study if no alternative medication was available or if the patient was unwilling to change medication. Imatinib systemic treatment was initiated at the Erasmus University Medical Center [Rotterdam, The Netherlands ($N = 31$)], University Medical Center Groningen [Groningen, The Netherlands ($N = 14$)], San Giuseppe Hospital [Empoli, Tuscany, Italy ($N = 4$)], and at the Santa Maria delle Croci Hospital [Ravenna, Italy ($N = 1$)]. Clinical data, including progression-free survival, were collected for patients treated in an incurable setting. This study was approved by the medical ethics review boards and conducted in accordance with the Declaration of Helsinki. This trial was registered at the International Standard Randomized Controlled Trials Number Register (ISRCTN63855172).

Pharmacokinetic sample collection

Blood samples for imatinib pharmacokinetic evaluation were collected on the first day of imatinib treatment and after 1, 6, and 12 months. On these days, blood samples were collected immediately before imatinib administration and 30 minutes, 1, 2, 3, 4, 6, and 24 hours after imatinib intake. In addition, on day 14, and

monthly during imatinib treatment, trough samples were taken to assess minimal imatinib plasma concentrations. The trough samples were taken just before the next day administration.

Methods for blood sample processing and storage, as well as analytic imatinib quantification, were described previously (14). A total of 1,820 imatinib plasma concentrations were considered for analysis. Ten samples were missing a concentration value (below the limit of quantification or assay error) and 67 trough samples were excluded as the time for sampling and/or the time for the preceding dose could not be determined exactly. Of the 1,743 observations that remained available for pharmacokinetic model building, 512 observations from 69 occasions were coupled to measurements on volume of liver metastasis and on the metastasis/liver volume ratio.

Population pharmacokinetic model

Observed imatinib plasma concentrations were log transformed before being used for parameter estimation. The use of log-transformed data during model building (transform-both-sides approach) resulted in a more stable estimation process. Compartmental models with linear and nonlinear processes were evaluated. As no intravenous data were available, the initial bioavailability (F) was set to 1, meaning that clearance and volume of distribution (V) should be interpreted as the clearance (CL/F) and apparent volume of distribution (V/F), respectively.

The population pharmacokinetic analysis was conducted using nonlinear mixed effects modelling in the NONMEM software (version 7.1.2, ICON Development Solutions). The ADVAN5 subroutine combined with the first order conditional estimation method with interaction between random effects was used in the model building procedure. Perl-speaks NONMEM (version 3.2.12, <http://psn.sourceforge.net/>) and the R-package Xpose (version 4.3.0, <http://xpose.sourceforge.net/>) were used to automate model runs and for graphical analysis.

Presence of liver metastases was used as a dichotomous covariate (LIV) in the analysis. Time dependency (TIME), body weight (WT), volume of liver metastasis (LIVM), and liver metastatic volume proportional to liver volume (LIVR) were evaluated as continuous covariates. Also the medical center, in which patients were treated (CENTER), was analyzed as a covariate. As the number of patients from the 2 Italian centers was small, those 2 centers were grouped as one. Potential CYP-interactive drugs were highly restricted in this study. Hence, as major interactions were not expected, comedication was not included as a covariate. Recorded imatinib doses were used for modelling and when information was missing, it was assumed there was no change in the dosing until the next recorded dose. As only a minority of drug activity is attributable to CGP74588, this metabolite was not included in the model.

Interindividual variability (IIV) for an individual (ind) was modeled exponentially, and the residual errors for observed concentrations (c_{obs}) versus predicted

concentrations (c_{pred}) on the log scale were modelled using an additive error.

The NONMEM objective function value (OFV), which is proportional to $-2 \times \log$ likelihood of the data, was used to evaluate different model structures. A difference in OFV of at least 6.63 (corresponding to $P < 0.01$) was used to discriminate between competing models. NONMEM SEs were complemented with asymmetric confidence intervals by log-likelihood profiling (LLP) and a bootstrap ($N = 1,000$; stratified on LIV; <http://psn.sourceforge.net/>). A visual predictive check (VPC) was done to evaluate the predictive performance of the model. The observed data was overlaid with a 90% prediction interval based on 1,000 simulated data sets from the final model. The VPC was stratified on months of each 24-hour pharmacokinetic sampling in the following way; group 0 (day 1), group 1 (month 1, 2, and 3), group 2 (month 5 and 6), and group 3 (months ≥ 11).

In addition, to assess imatinib metabolic ratios (AUC_{tau} CGP74588/ AUC_{tau} imatinib) at start of therapy and after 6 and 12 months of treatment, a noncompartmental analysis of our steady-state imatinib and CGP74588 pharmacokinetic data after 1, 6, and 12 months was conducted, using WinNonlin software (Phoenix WinNonlin version 6.1, Pharsight Corporation).

Computed tomographic-guided volumetric assessment of liver metastases

Original Digital Imaging and Communications in Medicine (DICOM) files were imported in the open source OsiriX Imaging Software for MacOSX (OsiriX Foundation). All available computed tomographic (CT) scans at baseline, 6, and 12 months of treatment were studied (15). Two regions of interest (ROI) were assessed per CT slice: total liver area and liver metastasis area. Total liver areas were manually outlined by using the closed polygon selection tool and liver metastases lesions were drawn with the pencil selection tool, which allows a more precise drawing (Appendix A; ref. 15). Volumes of all 3-dimensional structures were then automatically calculated (Appendix A; ref. 15). For metastases visualized in only one CT slice, the area was multiplied with slice thickness (5 mm) to estimate the volume. The gallbladder and the inferior vena cava were excluded from the ROI; intrahepatic biliary and vascular structures were included. The ratio of metastasis volume to liver volume was then calculated on the basis of the above described volumetric assessments.

Results

Patients

Twenty-nine male and 21 female patients were included in this population pharmacokinetic analysis. Median follow-up period was 366 days (range, 59–761 days); 26 patients (13 males, 13 females) had evaluable liver metastases. Median volume of liver metastases was 5.8 cm^3 (range, $0.68\text{--}1,800 \text{ cm}^3$) and the median metastasis/liver volume ratio was 0.42% (range, 0.042%–61%). See Table 1 for clinical characteristics.

Table 1. Patient characteristics ($N = 50$)

Characteristic	No. (%)
Median age (years)–range	61 (39–82)
Sex	
Male	29 (58)
Female	21 (42)
Primary cancer site	
Stomach	28 (56)
Rectum	9 (18)
Small intestine	8 (16)
Unknown	5 (10)
Disease	
Locally advanced	17 (34)
Metastatic	31 (62)
Liver	28 (56)
Intraperitoneal	22 (44)
Retroperitoneal	2 (4)
Other	4 (8)
Adjuvant setting	2 (4)
Histology	
Spindle cell	28 (56)
Epitheloid	13 (26)
Mixed	5 (10)
Unknown	4 (8)
Imatinib dose	
400 mg per day at start	50 (100)
Dose escalation during treatment	
To 600 mg per day	1 (2)
To 800 mg per day	13 (26)
Median ASAT (U/L) – range	24 (12–145)
Median ALAT (U/L) – range	22 (5–274)
Median ALP (U/L) – range	91 (47–847)
Median GGT (UL) – range	32 (10–613)
Median total bilirubin ($\mu\text{mol/L}$) – range	9 (3–39)

Abbreviations: ASAT, Aspartate aminotransferase; ALAT, alanine aminotransferase; ALP, Alkaline phosphatase; GGT, Gamma-glutamyltransferase.

Imatinib pharmacokinetics: time dependency

A 2-compartment model with linear elimination and 5 transit compartments to describe the absorption process (Fig. 1) best fitted observed imatinib plasma concentrations. In addition, the relative F and absorption rate (k_a) were both found to be significantly ($\Delta\text{OFV} = -246.4$) time-dependent according to:

$$F = 1 + \theta_F \times \exp(-\lambda \times \text{TIME}/24)$$

$$k_{a,\text{ind}} = (1 + \theta_{k_a} \times \exp(-\lambda \times \text{TIME}/24)) \times k_{a,\text{pop}} \times \exp(\eta k_{a,\text{ind}})$$

where TIME is the time in hours from first dose administration and λ the decay constant, which was found to have

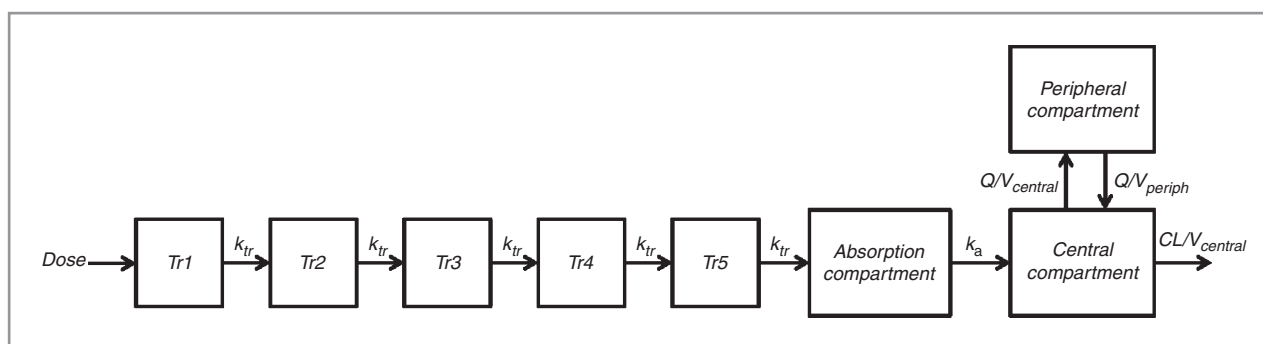


Figure 1. Imatinib population pharmacokinetic model. A, 2-compartment model with linear absorption and elimination and 5 transit compartments best fitted observed imatinib plasma concentrations. Abbreviations: Tr, transit compartments; k_a , absorption (L/h); Q, inter-compartmental clearance (L/h).

the same value for both parameters. θ_F and θ_{k_a} were more than 0 indicating that F and $k_{a,ind}$ start at a value of $1 + \theta_F$ and $k_{a,pop} \times (1 + \theta_{k_a})$, respectively, and both decrease with time to values of 1 and $k_{a,pop}$, respectively. Time dependence on F and k_a could be replaced with time dependence on CL and k_a (increasing CL with time) with an almost equally good fit ($\Delta OFV = +4.3$). However, this model was not robust and it was highly sensitive to initial parameter estimates, and quantitative testing of covariate effects could not be conducted. The predicted decreases in F and k_a as function of time after treatment start are shown in Fig. 2. After 30 days of treatment, F decreased with 17.4%, and after 90 days of treatment with 29.3%, compared with baseline. After 6 months and after 1 year, F decreased slowly further, with 32.2% and 32.5% compared with baseline (Fig. 2).

Noncompartmental analysis of our steady-state imatinib and CGP74588 pharmacokinetic data after 1, 6, and 12 months showed that the metabolic ratio ($AUC_{tau} CGP74588 / AUC_{tau} imatinib$) remained stable over time (mean metabolic ratios \pm SD at 1, 6, and 12 months: 0.72 ± 0.12 ; 0.75 ± 0.11 ; 0.74 ± 0.11 , respectively).

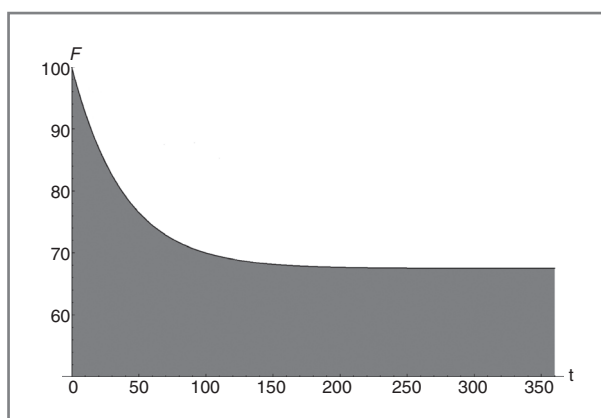


Figure 2. Predicted reduction in the relative bioavailability, F , over time. Assuming that the true bioavailability is equal to 100% at day 1, the predicted decrease can be understood by looking at percentage ratio ($F\%$ ratio) after 30, 90, 180, and 360 days. Abbreviations: $F\%$ -ratio, bioavailability percentage ratio; k_a , absorption (L/h); t , time (days)

Imatinib pharmacokinetics: liver metastasis dependency

Covariates WT, LIV, LIVM, and LIVR were tested on CL, $V_{central}$, and F . CENTER were tested on CL, F , and k_a . LIVM on CL gave the largest drop in OFV ($\Delta OFV = -21.8$), whereas the dichotomous covariate LIV was not significantly correlated with CL ($\Delta OFV = -0.4$). The effect of LIVM could not be associated with the parameters β_F or λ , governing time dependence on F . Combining the effect of LIVM in CL with an effect of LIVM also in F was not significant ($\Delta OFV = 0.0$). LIVR on CL was also significant ($\Delta OFV = -11.0$) but was not significant ($\Delta OFV = -2.3$) when combined with LIVM. Although including LIVM reduced the proportional residual error ϵ from 35.4% to 35.0%, it did not reduce the IIV in CL.

WT on CL gave a significant drop in OFV ($\Delta OFV = -13.9$), but was omitted in the final model because of too much data imputation. CENTER had no significant effect on CL ($\Delta OFV = -0.09$), F ($\Delta OFV = -0.97$) or k_a ($\Delta OFV = -3.74$) for 2 additional degrees of freedom, in which a difference in OFV by at least 5.99 corresponds with a significance level of $P < 0.05$.

The estimates of the final population pharmacokinetic model comprising the effect of LIVM on CL are presented in Table 2 together with NONMEM relative SEs (RSE), 95% confidence interval (CI) from the LLP and the median and 2.5 to 97.5 percentiles from 993 bootstrap replicates. The predicted decrease in CL as function of LIVM is expressed as:

$$CL_{POP} = 9.12 \times (1 - 0.000381 \times LIVM)$$

This means that for every 100 cm^3 increase in metastasis volume CL is decreased by 3.81%. The effect on apparent oral CL for the minimum (0.68 cm^3), median (5.8 cm^3), and maximum (1,800 cm^3) metastasis volume of the study population is 9.12 L/h, 9.10 L/h, and 2.87 L/h, respectively.

Effects of pharmacokinetics on clinical outcome

As shown in Appendix B, no statistically significant effects of pharmacokinetics on progression-free survival were found in the subset of patients treated with imatinib in an incurable setting. As this study was not

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Table 2. Parameter estimates for the final population pharmacokinetic model

Parameter	Estimate	RSE ^a (%)	Log-likelihood profiling 95% CI	Estimates based on 993 bootstrap replicates stratified on LIV = 0/1	
				Median	2.5–97.5 percentiles
CL (L/h)	9.12	7.5	7.94–10.5	9.13	7.76–10.6
V _{central} (L)	128	18	95.8–165	130	96.0–165
Q (L/h)	24.9	13	19.0–31.9	25.3	18.2–34.9
V _{periph} (L)	197	15	145–265	202	142–276
k _a (1/h)	0.699	20	0.510–0.942	0.710	0.502–1.05
k _{tr} (1/h)	15.8	17	10.9–24.9	15.4	11.3–22.8
Residual error, ε (%)	35.0	6.4	33.6–36.5	34.5	30.3–39.2
θ_F	0.482	26	0.367–0.610	0.511	0.225–0.865
θ_{k_a}	1.18	28	0.72–1.82	1.15	0.525–1.97
λ (1/day)	0.0256	37	0.0181–0.0357	0.0258	0.0143–0.0565
θ_{LIVM} (1/cm ³)	0.000381	3.9	0.000290–0.000440	0.000383	-0.000300–0.00124
IIV CL (CV%) ^b	49.5	26 ^c	39.6–64.3	49.0	36.8–63.4
IIV V _{central} – k _a (CV%) ^b	70.9	26 ^c	50.7–104	70.4	46.9–97.0
IIV k _{tr} (CV%) ^b	160	25 ^c	104–314	153	97.0–263
IIV V _{periph} (CV%) ^b	65.9	33 ^c	39.9–107	67.1	34.6–97.6

Abbreviations: LIV, dichotomous covariate indicating presence or absence of liver metastasis; CL, apparent oral clearance; V_{central}, volume of distribution for the central compartment; Q, intercompartmental clearance; V_{periph}, volume of distribution for the peripheral compartment; k_a, absorption rate constant; k_{tr}, transit rate constant between the transit compartments; θ_F , change in bioavailability relative start of treatment; θ_{k_a} , change in absorption rate relative start of treatment; λ , decay constant; θ_{LIVM} , variability based on liver metastatic volume; IIV CL, interindividual variability in apparent oral clearance; IIV V_{central} – k_a, interindividual variability in volume of distribution for the central compartment and absorption rate constant; IIV k_{tr}, interindividual variability in the transit rate constant between compartments; IIV V_{periph}, interindividual variability in volume of distribution of the peripheral compartment.

^aRelative Standard Error given by NONMEM

^bCoefficient of Variation, calculated as $(\exp(\omega^2) - 1)^{0.5}$

^cRSE is related to the corresponding variance term, ω^2

designed to study outcome, it is impossible to draw hard conclusions on associations between pharmacokinetics and survival.

Validation of the final population pharmacokinetic model

NONMEM RSEs, LLP 95% CIs, and bootstrap 2.5 to 97.5 percentiles are in good agreement for most parameters, the notable exception being the covariate parameter θ_{LIVM} for which the bootstrap percentiles contain the 0-value, whereas this is not the case for the corresponding LLP CI.

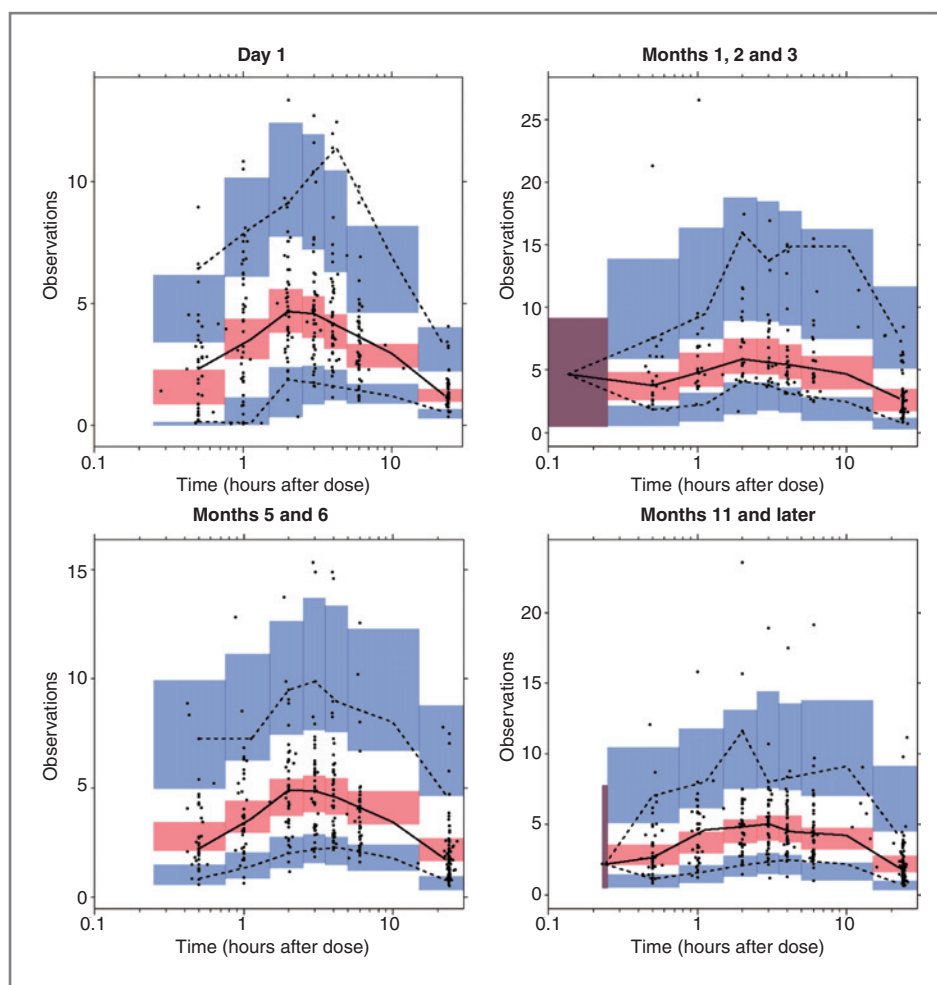
Visual predictive checks based on 1,000 simulations are shown in Fig. 3. Observed imatinib plasma concentrations (in $\mu\text{mol/L}$) showed good agreement with the 95% CIs for the 5th, 50th, and 95th percentiles of the simulated predictions. Time after dose (in hours) was used as the independent variable.

Discussion

This is the first prospective population pharmacokinetic study in patients with GIST, analyzing imatinib pharmacokinetics over an extensive median follow-up period of one year. During this study period, the reached number of

follow-up pharmacokinetic observations was several times larger than in previous retrospective imatinib population pharmacokinetic studies in patients with GIST, expressing the validity of the current data (11, 16). A multicompartmental pharmacokinetic model was built by use of this pharmacokinetic data set, showing a significant downward trend in systemic exposure to imatinib over time. From start of therapy up to 90 days, the initial imatinib exposure is reduced by approximately one third. From this time point on, the curve flattens, suggesting a further steady imatinib pharmacokinetics. Previous retrospective associations between imatinib trough levels at day 29 and clinical outcome benefit in patients with GIST thus need to be put into this perspective (10). As the predicted decrease in imatinib exposure at this time point is approximately 17%, the distribution of patients in groups based on imatinib trough levels will differ from the distribution seen after 3 months, when predicted systemic exposure to imatinib has dropped by approximately 30%. Within this 90-day period, significance of correlations between pharmacokinetics-based groups and clinical benefit will fluctuate. However, provided the proposed clinically relevant imatinib threshold level of 1,100 ng/mL is accurate, a number of patients will experience a drop below the efficacious plasma

Figure 3. VPCs based on 1,000 simulations for imatinib plasma concentrations in $\mu\text{mol/L}$ as function of time after dose in hours. The VPC was stratified on months after start of treatment for each 24-hour pharmacokinetic sampling in the following way: group 0 (day 1), group 1 (month 1, 2, and 3), group 2 (month 5 and 6), and group 3 (months ≥ 11). Legend: dots, real imatinib observations; solid and dashed lines, the 50th, 5th, and 95th percentiles for all real observations in each bin. Red and blue shaded areas denote the 95% CI for the 50th, 5th, and 95th percentiles of the simulated data.



level after day 29 of imatinib therapy and may thus be underdosed when trough levels are only assessed after the first month of therapy. In addition, a delayed dose escalation might potentially be valuable in patients dropping below this threshold level. On the other hand, the proposed threshold may only be a marker for the actual clinically relevant imatinib plasma concentration cutoff value, which is reached after 3 months. This is highly relevant if therapeutic drug monitoring should be applied in future imatinib dosing. Imatinib plasma level monitoring in patients with GIST should therefore be time point-specific and repeated after the first quarter of the first year of imatinib treatment. This will have to be taken into account when designing randomized studies aimed to validate the use of imatinib plasma level monitoring, that up to that validation will have to be considered as investigational. Our data also provide a plausible explanation for the lack of decreased imatinib pharmacokinetics in patients with GIST in a recent retrospective pharmacokinetic analysis, as the median time from start of therapy to first pharmacokinetic assessment in this study was 5.5 months (16). In light of our findings, a major drop in imatinib plasma levels has already occurred during this lag time.

Currently, literature on mechanisms that may drive these acquired pharmacokinetic phenomena in imatinib-treated patients is scarce (17). Visually, maximum imatinib plasma concentrations in our study population (C_{\max}) are lower and time to reach C_{\max} is longer after 3 months of dosing (Fig. 3) as compared with the first 3 months of treatment. In addition, the final pharmacokinetic model fitted significantly better when adding a time dependence in absorption rate as a covariate (OFV = -42.9). These observations suggest that the observed time-dependent drop in imatinib exposure is located at the absorption phase. Hence, there may be a change in activity or expression of drug transporters involved in facilitated or active transport of imatinib. However, drug uptake and efflux transporters have shown a limited effect on imatinib absorption and excretion (17, 18), and *in vivo* data showed no upregulation of drug efflux transporters after long-term treatment with imatinib (19). So, up until now, key mediators of imatinib transport during absorption and elimination have not been identified. On the other hand, as imatinib is extensively metabolized by CYP3A4 to its main metabolite CGP74588 (13), upregulation of liver enzymatic function may also (in part)

account for the observed drop in imatinib plasma levels. This pharmacokinetic mechanism would possibly have a minor impact on imatinib efficacy as CGP74588 is equipotent to its parent compound and has a longer terminal elimination half-life (20). However, metabolic ratios ($AUC_{\text{tau}} \text{ CGP74588} / AUC_{\text{tau}} \text{ imatinib}$) remained stable during the first year of treatment, implying that upregulation of metabolic activity does not occur over time. Finally, increasing patient nonadherence to imatinib treatment over time may also be involved in the observed decline in systemic exposure. This is less likely to be of large influence on exposure though, as full pharmacokinetic time-profiles show limited accumulation (a limited effect of single imatinib trough levels on total exposure). Occasional dosing delays will therefore have a limited effect on imatinib exposure. Moreover, an observational study evaluating compliance in 28 imatinib-treated GIST patients at 2 time points, detected no significant difference in nonadherence rates after 90 days of imatinib use (21).

Secondary objective of this study was to evaluate if volume of liver metastasis in patients with GIST is predictive for imatinib exposure. Liver metastasis volume seemed to have a minor effect on imatinib CL/F , rendering some clinical significance with massive liver involvement, as for every 100 cm³ increase of metastatic volume, a predicted decrease of approximately 4% in CL/F is observed. This is in concordance with an earlier phase I side study that reported limited effect of liver dysfunction on imatinib exposure (22). These data together with our present results indicate that neither liver metastatic involvement nor routine liver function testing highly correlate with hepatic CYP activity in imatinib-treated patients.

To conclude, this observational population pharmacokinetic study shows that imatinib pharmacokinetics in patients with GIST stabilizes after approximately 3 months of dosing with a significant decrease in systemic exposure of approximately 30% compared with baseline, most likely due to reduced absorption. This means that future "trough level to clinical benefit" analyses should be time point-specific and need to incorporate relevant tumor biology and patient characteristics in multivariate analyses. Such survival analyses based on imatinib pharmacokinetics should be

conducted in large (multicenter) patient populations and could, ultimately, lead to therapeutic fine tuning in which a minimal effective imatinib dose for an individual patient can be defined on accurate time points in a treatment course.

Disclosure of Potential Conflicts of Interest

A.K.L. Reyners and W.T.A. van der Graaf are consultant/advisory board members of Novartis and W.T.A. van der Graaf has a commercial research grant from Novartis. No potential conflicts of interest were disclosed by the other authors.

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