Pharmacokinetic-Pharmacodynamic Relationships of Imatinib and Its Main Metabolite in Patients with Advanced Gastrointestinal Stromal Tumors

Catherine Delbaldo,[1] Etienne Chatelut,[2] Micheline Ré,[3] Alain Deroussent,[4] Sophie Séronie-Vivien,[2] Aurore Jambu,[2] Patrice Berthaud,[6] Axel Le Cesne,[5] Jean-Yves Blay,[7] and Gilles Vassal[3]

Abstract

Purpose: This study explored factors affecting the pharmacokinetic variability of imatinib and CGP 74588, and the pharmacokinetic-pharmacodynamic correlations in patients with advanced gastrointestinal stromal tumors.

Experimental Design: Thirty-five patients with advanced gastrointestinal stromal tumors received 400 mg of imatinib daily. Six blood samples were drawn: before intake, during 1- to 3- and 6- to 9-hour intervals after intake on day 1, and before intake on days 2, 30, and 60. Plasma imatinib and CGP 74588 concentrations were quantified by reverse-phase high-performance liquid chromatography coupled with tandem mass spectrometry, and analyzed by the population pharmacokinetic method (NONMEM program). The influence of 17 covariates on imatinib clearance (CL) and CGP 74588 clearance (CLM/fm) was studied. These covariates included clinical and biological variables and occasion (OCC = 0 for pharmacokinetic data corresponding to the first administration, or OCC = 1 for the day 30 or 60 administrations).

Results: The best regression formulas were: CL (L/h) = 7.97 $(AAG/1.15)^{-0.52}$, and CLM/fm (L/h) = 58.6 $(AAG/1.15)^{-0.60} \times 0.55^{OCC}$, with the plasma α1-acid glycoprotein (AAG) levels indicating that both clearance values decreased at a higher AAG level. A significant time-dependent decrease in CLM/fm was evidenced with a mean (+SD) CGP 74588/imatinib area under the curve (AUC) ratio of 0.25 (±0.07) at steady state, compared with 0.14 (±0.03) on day 1. Hematologic toxicity was correlated with pharmacokinetic variables: the correlation observed with the estimated unbound imatinib AUC at steady-state ($r = 0.56$, $P < 0.001$) was larger than that of the total imatinib AUC ($r = 0.32$, NS).

Conclusions: The plasma AAG levels influenced imatinib pharmacokinetics. A protein-binding phenomenon needs to be considered when exploring the correlations between pharmacokinetics and pharmacodynamics.

Imatinib (Glivec, Gleevec), a phenylaminopyrimidine derivative, is a highly selective inhibitor of the protein kinase family comprising bcr-abl, platelet-derived growth factor, and the product of the c-kit proto-oncogene (1, 2). c-kit is a transmembrane tyrosine kinase receptor for the ligand stem cell factor found in a variety of normal and tumor cells. Gastrointestinal stromal tumors (GIST) are mesenchymal tumors of the digestive tract originating from the interstitial cells of Cajal (3). They are characterized by c-kit expression and have a high incidence of activation, gain of function, and mutation of c-kit (4–6). Imatinib is extensively metabolized by the cytochrome P450 enzyme system; liver CYP3A4 is the main enzyme responsible for imatinib metabolism. CGP 74588, the main circulating metabolite formed by CYP3A4, is an *N*-desmethylated piperazine derivative endowed with *in vitro* activity comparable to that of imatinib (4).[8] Prior pharmacokinetic analysis showed that imatinib displayed linear pharmacokinetics with proportional drug accumulation in patients with advanced GIST (5).

Despite the spectacular clinical activity of imatinib, 10% of patients with advanced GIST exhibit primary resistance to the drug and 20% develop secondary resistance under imatinib treatment (6–10). Resistance is partly dependent on c-kit mutations, however, low imatinib exposure [i.e., plasma area

Authors' Affiliations: [1]Hospital Henri-Mondor, Créteil, France, [2]EA3035, Institut Claudius-Regaud, Toulouse, France, [3]Pharmacology and New Treatment of Cancer, UPRES EA3535, [4]Mass Spectrometry Facility, and [5]Department of Medicine, Institut Gustave-Roussy, Villejuif, France, [6]Novartis Pharma, France, and [7]Centre Léon-Bérard, Lyon, France

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Requests for reprints: Gilles Vassal, Pharmacology and New Treatment of Cancer, UPRES EA 3535, Institut Gustave-Roussy, 39 rue Camille Desmoulins, 94805 Villejuif Cedex, France. Phone: 33-14211-4947; Fax: 33-14211-5308; E-mail: gvassal@igr.fr.

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[8] Novartis Pharma Stein AG. Gleevec (imatinib mesylate): prescribing information (online). Available from http://www.gleevec.com/info/page/prescribing info (accessed March 2, 2006).

under the curve (AUC)] is a possible mechanism of resistance (9–11). One trial explored the pharmacokinetic and pharmacodynamic relationships of imatinib in patients with chronic myeloid leukemia (5). The model described in that study did not fully explore hematologic response, and in particular, the resistance acquired after an initial response, and the authors were unable to characterize the pharmacokinetic-pharmacodynamic relationship between drug exposure and clinical outcome. Another trial in patients with advanced GIST explored the pharmacokinetics, and reported considerable interpatient variability in drug exposure with an unexplained coefficient of variation ranging from 40% to 60% (12).

Imatinib is well-tolerated compared with conventional chemotherapy. Its main toxicities are edema (periorbital, face, and limbs), cutaneous rash, and anemia. Some patients develop more severe or unexpected toxicity (13). A dose-toxicity relationship is suspected based on clinical observations after comparing low and high doses of imatinib, but these studies yielded controversial results and no definitive conclusions could be drawn (8, 14).

This study was designed to explore the pharmacokinetic-pharmacodynamic relationships of imatinib in terms of clinical activity and tolerance in patients with advanced GIST, in the context of the French Sarcoma Group, BFR 14 phase III trial exploring treatment duration (15). We also explored covariates affecting the pharmacokinetic variability of imatinib and CGP 74588.

Materials and Methods

Patients

Patients with metastatic and/or unresectable malignant GIST who had relapsed were enrolled in the French Sarcoma Group, BFR 14 phase III trial (15). At the end of a 1-year treatment period, patients without progressive disease were randomized between discontinuation or maintenance of imatinib. When patients who had discontinued imatinib relapsed, the treatment was reinitiated. Study eligibility criteria were as follows: histologically documented diagnosis of advanced/metastatic GIST, immunohistochemically documented c-kit (CD117) expression either in the primary tumor or metastases using the DAKO assay, age ≥18 years, Eastern Cooperative Oncology Group performance status (0-3), adequate bone marrow function (absolute neutrophil count >1.0 × 10^9/L, platelets >100 × 10^9/L), serum creatinine value <1.5× the upper limit of normal, total bilirubin level <1.5× the upper limit of normal, glutamate oxaloacetate transaminase and glutamate pyruvate transaminase <2.5× the upper limit of normal (or <5× the upper limit of normal if hepatic metastases is present), no chemotherapy or major surgery within 2 weeks before study entry, no intercurrent history of uncontrolled severe dysfunction, grade III/IV cardiac problems defined by the New York Heart Association or a known diagnosis of HIV, no other previous tumor within 3 years except basal cell skin cancer or cervical *in situ* carcinoma, a negative pregnancy test for women with a child-bearing potential, and a signed informed consent.

Complete medical histories, a physical examination, and laboratory tests were done at baseline and at each scheduled visit: a complete blood count with differential, creatinine, serum electrolytes, calcium, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, glutamate pyruvate transaminase, glutamate oxaloacetate transaminase, γ-glutamyl transferase, lactate dehydrogenase, prothrombin, activated partial thromboplastin time, and fibrinogen. The patients received 400 mg of Gleevec orally once a day, using the drug formulated as hard gelatin capsules. When disease progressed, doses were increased to 600 mg/d. If progression was confirmed after 2 months of the incremented dose, treatment was stopped. The dose was decreased to 300 mg/d if grade 3 toxicity occurred.

Pharmacokinetic study

Blood sampling and mass spectrometry analysis. Blood samples for pharmacokinetic purposes were drawn after the first dose and on days 30 and 60. Plasma samples were collected before drug intake, between 1 and 3 hours, between 6 and 9 hours, and 24 hours after imatinib intake (day 1), and at 1 (day 30) and 2 months (day 60) of treatment (before imatinib intake). Whole blood (5 mL) was collected in heparinized tubes and centrifuged within 30 minutes at 4,000 × *g* for 15 minutes at 4°C, and 2.5 mL of plasma were transferred into propylene ice-cold tubes and stored at −20°C, until analysis.

Imatinib, CGP 74588, and the internal standard (imatinib-D8) were kindly provided by Novartis Pharma AG (Basel, Switzerland). Quantitative analyses of imatinib and CGP 74588 were done using reverse-phase high-performance liquid chromatography with fluorescence detection and coupled with tandem mass spectrometry as published elsewhere (16). Ten microliters of the standard, control, and patient samples were analyzed by the LC system (pomp HP1100 model; HP/Agilent Technology, and a detector quattro LCZ; Micromass, Chicago, IL). The analyses were done with Masslynx, version 3.4. The lower limit of quantification for both imatinib and CGP 74588 was 10 ng/mL.

Plasma α1-acid glycoprotein analysis. Plasma α1-acid glycoprotein (AAG, in g/L) was measured by an automated turbidimetric immunoassay in which precipitation was enhanced by polyethylene glycol. Absorbance was measured at 340 nm. The analyzer (Konelab 60i) as well as controls, standards, antiserum, and associated reagents were from the Thermo Electron Corporation (Helsinki, Finland). As in the case of other biological covariates, AAG values were determined at each stage of the pharmacokinetics study (days 1, 30, and 60).

Population pharmacokinetic analysis. Plasma imatinib and CGP 74588 concentrations were analyzed according to a nonlinear mixed effects ("population") approach using the NONMEM program (version V, level 1.1) running on a PC (Pentium 200 pro) using the first order method (alternative estimation methods such as FOCE and FOCE INTERACTION did not allow successful minimization; ref. 17). A proportional error model was used for both interpatient and residual variability. The influence of the 17 following covariates on pharmacokinetic variables was examined: age, gender, body weight, serum creatinine, creatinine clearance (calculated according to the Cockcroft-Gault equation), albuminemia, proteinemia, bilirubinemia, the plasma AAG level, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, C-reactive protein, the presence of edema or liver metastasis, hemoglobinemia, WBC count, and occasion (OCC), with OCC equal to 0 if pharmacokinetic data were obtained after the administration on day 1, or equal to 1 after imatinib intake on days 30 and 60. For biological covariates (e.g., AAG), the specific value at each stage of the pharmacokinetics study (days 1, 30, or 60) was used for the data analysis. First, the influence of each covariate on total plasma clearance of imatinib (CL) was tested according to the following equation using AAG, for example: $CL = \theta 1\ (AAG/\text{mean } AAG)^{\theta 2}$, where θ1 is the typical value of CL for a patient with the mean covariate, and θ2 is the estimated influential factor for AAG. Full and reduced models (one variable less) were compared by the χ^2 test of the difference between their respective objective function values. The objective function value is equal to minus twice the log likelihood of the data. This value is an indicator of the goodness of fit of the model. A change of at least 3.84 ($P < 0.05$, 1 degree of freedom) was required for a covariate to be considered significantly correlated with the pharmacokinetic variable (log-likelihood test). Secondly, an intermediate model including all significant covariates was obtained. A stepwise backward elimination procedure was carried out. At both steps, the interindividual variability estimate and the change in the objective function value were considered in order to assess the effect of each covariate. The log-likelihood test was also used to select the structural pharmacokinetic

model. The population pharmacokinetics model for imatinib was defined, and the corresponding final pharmacokinetic variables (means and variances from the model included the effect of covariates on imatinib variables) were fixed while developing the CGP 74588 pharmacokinetic model. A bioavailability (F) of 1 was assumed in the absence of i.v. drug administration data.

Systemic exposure (i.e., AUC) to imatinib and to CGP 74588 was calculated using individual POSTHOC clearance: AUC = dose/CL for imatinib, and AUCm = dose / (CLm/fm) for CGP 74588 on days 1, 30, and 60.

Pharmacodynamic analysis. Toxicity was evaluated weekly for 2 months, then monthly for 4 months, and then every 3 months, and graded using the National Cancer Institute's Common Toxicity Criteria, version 2.0. Hematologic toxicity was also measured by the relative decrease in the absolute neutrophil count (ANC), in hemoglobin, and in platelets [e.g., % ANC = (ANC nadir − ANC on day 1) / ANC on day 1]. Tumors were evaluated and/or measured at baseline by CT scan and reassessed every 2 months using WHO standard criteria (Response Evaluation Criteria in Solid Tumors). We assessed the correlation between systemic exposure to imatinib and/or CGP 74588 and response and toxicity, and the correlation between the plasma AAG level on days 1, 30, and 60 and response and toxicity, using GraphPad Prism InStat 3.00 for Windows 95 (GraphPad Software, San Diego, CA).

Statistics

Statistical comparisons to study the pharmacokinetic-pharmacodynamic relationships (nonparametric Mann-Whitney and Pearson tests) were done using GraphPad Prism InStat 3.00 for Windows 95. Two-sided $P < 0.05$ was considered significant.

Results

Patients. Thirty-five patients (26 males; median age, 55 years; range, 28-84 years) with a metastatic [$n = 33$, liver metastases ($n = 15$), sarcomatosis ($n = 10$), and both liver metastases and sarcomatosis ($n = 8$)] or an unresectable ($n = 2$) GIST expressing c-kit were enrolled in the French Sarcoma Group, BFR 14 phase III trial (15). Patient characteristics are summarized in Table 1. They received a once daily 400 mg dose of Gleevec and no dose increment or decrease was required due to progression or toxicity, during the 2-month pharmacokinetic study. One patient died of tumor progression within a month of inclusion and a complete pharmacokinetic analysis could not be done. To date, 73 patients have been included in the BFR 14 trial and complete data on response, tolerance, and extensive follow-up will be published elsewhere as the trial is still ongoing (15).

Pharmacokinetics model and covariates. A total of 175 plasma samples were available, but only 166 samples from 34 patients were taken into account for the population pharmacokinetics analysis. Nine concentrations were unexpected values, probably due to poor patient compliance (observed concentrations <5% of values observed at the corresponding time in the same patients on another occasion). Pharmacokinetics were adequately described by a one-compartment model with zero-order absorption and first-order elimination (Fig. 1). This model was previously used by Schmidli et al. to analyze data from 371 patients (18). Moreover, alternative structural models (i.e., first-order absorption, two-compartment model) were not associated with a lower objective function value. The corresponding pharmacokinetic variables were: D1 (duration of zero-order absorption from the depot compartment), V (volume of distribution of imatinib), and CL (total plasma clearance of imatinib). The basic pharmacokinetic model for imatinib included interoccasion variability (IOV) exclusively on D1 (inclusion of IOV on CL or V was not associated with an improvement of the goodness of fit). During individual testing of the 17 covariates, 4 covariates (i.e., AAG, hemoglobinemia, albuminemia, and WBC) were significantly ($P < 0.05$) correlated with CL. A stepwise backward elimination procedure applied to the intermediate model including the four covariates identified AAG as the only significant covariate. Interindividual variability in CL, expressed by the coefficient of variation, decreased from 38% (no covariate) to 29% when AAG was taken into account, according to the following equation: $CL = \theta 1 \times (AAG / \text{mean } AAG)^{\theta 2}$ (Table 2). Residual variability was 22.4% for imatinib concentrations.

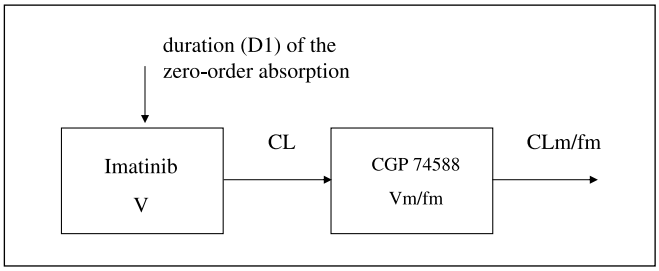

Fig. 1. Pharmacokinetic model: volume of distribution (Vm/fm) and clearance (CL/fm) of CGP 74588 were apparent variables with fm corresponding to the fraction of imatinib converted into CGP 74588.

Analysis of both plasma imatinib and CGP 74588 concentrations required an additional compartment and corresponding variables (Fig. 1): Vm/fm (apparent volume of distribution of CGP 74588), and CLm/fm (apparent total clearance of CGP 74588), where fm is the fraction of imatinib converted into CGP 74588. Residual variability was 26.7% for CGP 74588 concentrations. Four covariates (i.e., AAG, hemoglobinemia, albuminemia, and OCC) were significantly ($P < 0.05$) correlated with CLm/fm. The final covariate model obtained after a stepwise backward elimination procedure was: $CLm/fm = \theta 5\ (AAG/\text{mean } AAG)^{\theta 6} \times \theta 7^{OCC}$, with OCC equal to 0 if pharmacokinetic data were obtained on day 1, or equal to 1 on day ≥30. A significant decrease in apparent plasma clearance of the metabolite was evidenced over time (Table 2). OCC was not a significant covariate for any of the other imatinib or CGP 74588 pharmacokinetic variables. This model adequately predicted imatinib and CGP 74588 pharmacokinetic profiles (Fig. 2).

The AUC was calculated on days 1, 30, and 60 using specific POSTHOC clearances corresponding to those days for both imatinib and CGP 74588. Assuming that the relationships between the AAG level and the typical clearance value of either imatinib (CL) or CGP 74588 (CLm/fm) correspond to the

Table 1. Patient characteristics ($N = 35$)

	No. of patients
Male/female	26/9
Age, years mean (range)	55 (28-84)
Primary site gastric/ileal/other	9/12/14
Gastrectomy	10
Site of disease liver/sarcomatosis/ liver and sarcomatosis	15/10/8
WHO performance status 0/1/2	23/10/2

Table 2. Mean, interindividual, and interday variability, and covariate models of imatinib and CGP 74588 pharmacokinetic variables

Final covariate model*	Mean (±95% CI)	%CV†		
Imatinib				
Clearance: CL (L/h) = $\theta1$ (AAG/1.15)$^{\theta2}$	$\theta1$ = 7.97 (±0.93); $\theta2$ = −0.52 (±0.15)	29		
Volume of distribution: V (L) = $\theta3$	$\theta3$ = 168 (±35)	62		
Duration of zero order absorption: D1 = $\theta4$	$\theta4$ = 2.53 (±1.39)	80		
Interoccasion variability of D1		38		
CGP 74588				
Clearance: CLm/fm (L/h) = $\theta5$ (AAG/1.15)$^{\theta6}$ × $\theta7^{OCC}$	$\theta5$ = 58.6 (±5.6); $\theta6$ = −0.60 (±0.19); $\theta7$ = 0.55 (±0.05)	23		
Volume of distribution: Vm/fm (L) = $\theta8$	$\theta8$ = 15.4 (±3.21)	72		
Alternative covariate models	**Mean (±95% CI)**	**ΔOBJ‡**	***P***	**%CV†**
CL = $\theta1$	$\theta1$ = 8.13 (±1.26)	+62	<0.001	38
CLm/fm = $\theta5$	$\theta1$ = 44.1 (±8.5)	+135	<0.001	32
CLm/fm = $\theta5$ × $\theta7^{OCC}$	$\theta5$ = 54.6 (±7.9); $\theta7$ = −0.62 (±0.06)	+60	<0.001	36
CLm/fm = $\theta5$ (AAG/1.15)$^{\theta6}$	$\theta5$ = 43.3 (±4.8); $\theta6$ = −0.41 (±0.30)	+118	<0.001	21

Abbreviation: CI, confidence interval
*AAG: plasma AAG level (g/L); occasion with OCC equal to 0 if pharmacokinetic data were obtained on day 1, or equal to 1 on day ≥30.
†Coefficient of variation for interindividual variability (not explained by the covariate, if any) or interoccasion variability.
‡Change in objective function by comparison with the final covariate model.

relationships between the clearance of either CL or CLm/fm and the plasma unbound fraction of either CL or CLm/fm, the unbound AUCs (AUC_u and $AUCm_u$, for imatinib and CGP 74588, respectively) were estimated from these relationships: $AUC_u = AUC \cdot (AAG/1.15)^{-0.52}$ for imatinib, and $AUCm_u = AUCm \cdot (AAG/1.15)^{-0.60}$ for CGP 74588.

Pharmacokinetic-pharmacodynamic relationships. Twenty-three patients experienced grades 1 to 2 edema (face and lower limbs) but no grades 3 to 4 edema occurred. In 14 patients, edema appeared during the first month of treatment. One patient had to stop imatinib for a week after 1 month of treatment due to grade 2 liver toxicity. There were no dose reductions or increments in any patients during the 2-month pharmacokinetic study period. Complete data on safety will be reported elsewhere (15).

Individual imatinib and CGP 74588 AUCs (total or unbound) corresponding to the different days of pharmacokinetic investigations (days 1, 30, and 60) were compared with toxicity: the percentage of decrease in ANC (% ANC) or platelets (% platelets), and the occurrence of edema. The AUCs most correlated with hematoxicity were those of unbound imatinib: R^2 ranged between 0.27 and 0.32 for the ANC, and 0.17 and 0.20 for the percentage of platelets. The best observed correlation corresponded to the percentage of ANC versus imatinib AUC_u on day 30 ($P < 0.001$; Fig. 3A). For comparison purposes, percentages corresponding to the total imatinib AUC on the same day are shown in Fig. 3B (not significant). The occurrence of edema (23 of 34 patients) was not correlated with imatinib exposure (total and unbound fraction) neither on day 1 nor at 1 and 2 months of treatment.

Thirty-four of the 35 patients were evaluable for tumor response. Fifteen patients had stable disease (44%) and 16 patients achieved a partial response (47%) at 2 months. The response rate was not correlated with imatinib exposure (total and unbound AUC) neither on day 1 nor at 1 and 2 months of treatment.

The percentage of decrease in ANC (% ANC) was significantly correlated ($P < 0.01$; Fig. 4A) with plasma AAG on day 1, but not the percentage of decrease in platelets (% platelets; Fig. 4B, not significant). Plasma AAG at 1 and 2 months of treatment was not correlated with hematologic toxicity. Response and the occurrence of edema were not significantly

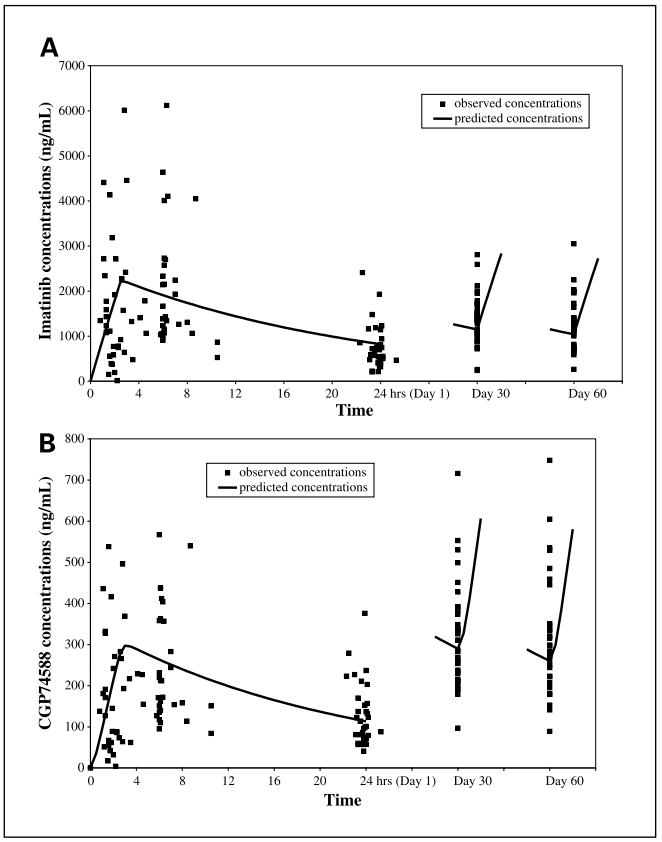

Fig. 2. Imatinib (*A*) and CGP 74588 (*B*) observed and predicted plasma concentrations (in ng/mL) versus time profiles.

correlated with any plasma AAG value, neither on day 1 nor at 1 and 2 months of treatment.

Discussion

Some studies have reported that an inflammatory response can modulate the pharmacokinetics of chemotherapeutic agents. Inflammation is one of the chief features of GIST, as is the case in many other tumors (19, 20). AAG is one of the proteins involved in the acute phase of an inflammatory reaction. It mediates response to proinflammatory stimuli aimed at restoring homeostasis via mainly cytokine pathways (21). AAG is extensively implicated in the protein binding of imatinib (22). At relevant clinical concentrations, ~95% of imatinib binds to AAG and to albumin. Moreover, data from chronic myeloid leukemia trials suggested that elevated AAG levels may result in a lower drug level in blast cells due to a decrease in the free fraction of imatinib (22, 23). Prior pharmacokinetic analyses showed that imatinib displayed linear pharmacokinetics with proportional drug accumulation in patients with advanced GIST, but reported considerable interpatient variability in drug exposure with a coefficient of variation ranging from 40% to 60% which was not adequately explained (5, 12). These data prompted us to examine the influence of the plasma AAG level on imatinib pharmacokinetic variables and on its clinical activity.

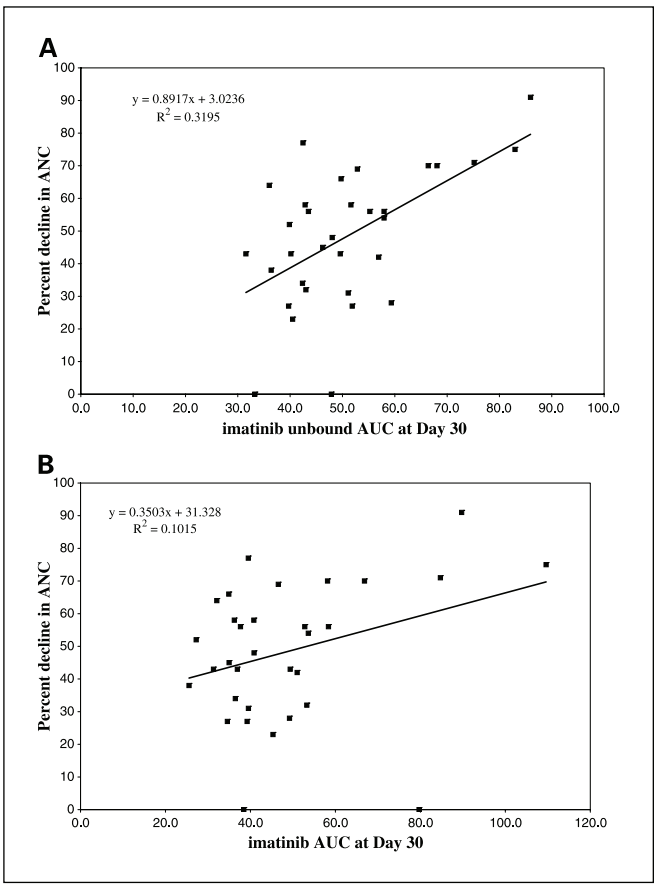

Fig. 3. Correlation between estimated imatinib unbound AUC (AUC_u, *A*) or imatinib total AUC (*B*) at day 30, and percentage of decrease in ANC.

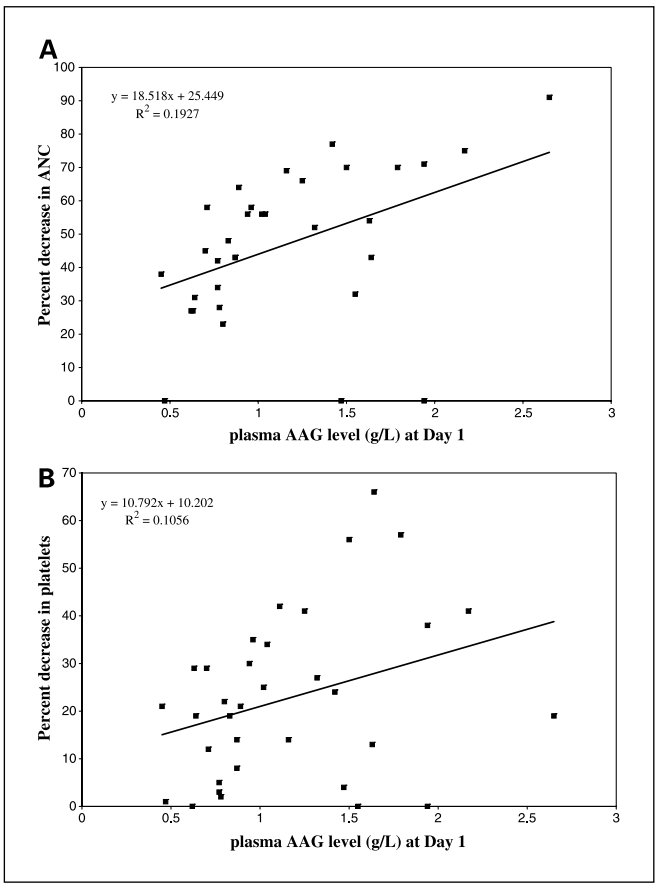

Fig. 4. Correlation between plasma AAG (in g/L) on day 1 and percentage of decrease in ANC (*A*) or percentage of decrease in platelets (*B*).

The mean pharmacokinetic variables obtained during this study were consistent with those previously reported: 8.1 versus 8.5 to 11.8 L/h[4] and 9.3 L/h[12] for the typical value of oral imatinib clearance; 0.25 to 0.14 (depending on the treatment period: days 1 or ≥30) versus 0.18 for the plasma CGP 74588/imatinib AUC ratio (4, 24). Although all patients received the same dose of imatinib, a wide dispersion of plasma concentrations of both imatinib and its metabolite was observed. The interindividual variability of both imatinib clearance and apparent CGP 74588 clearance decreased significantly from 38% to 29% and from 36% to 23%, respectively, when the plasma AAG value was included in the equations used to estimate the typical clearance values (CL and CLm/fm; Table 2). The higher the plasma AAG level, the lower the clearance of both imatinib and CGP 74588. As imatinib binds mainly to AAG, presumably its metabolite has the same binding site. Both are low extraction drugs eliminated by hepatic metabolism, and high plasma AAG levels limit the free fraction available for CL in the liver. Moreover, as expected, the pharmacokinetic-hematoxicity relationship was closer when the estimated unbound imatinib AUC (AUC_u; calculated from the individual total AUC and AAG level) was taken into account rather than the total AUC (Fig. 3A and B). All these results emphasize that further pharmacokinetic-pharmacodynamic studies of imatinib should include measurement of the unbound fraction of imatinib (or, at least, its estimation based on the AAG level).

In this study, a decrease in the apparent clearance of the metabolite (CLm/fm) was observed over time, with a lower value at steady-state than that observed after intake on day 1. However, as previously reported, no change in imatinib clearance (CL) was observed over time (12). No definitive explanation can be given based on our data because either a decrease in the elimination of CGP 74588 (CLm) or an increase in the fraction of imatinib converted into CGP 74588 (fm) may account for our finding. The second hypothesis is unlikely because it would have been associated with a parallel change in the apparent volume of distribution of the metabolite between day 1 and steady-state (Vm/fm) and a change in imatinib clearance (CL). Such changes were not observed. The first hypothesis may correspond to saturation of the metabolism of CGP 74588 when its concentration reaches a higher level due to the accumulation process.

Prior clinical observations suspected the existence of a dose-toxicity relationship and that the absolute dose was a good predictor of neutropenia (7). Other studies identified prognostic factors for toxicity. For example, a low hemoglobin level at baseline seemed to be predictive of hematologic toxicity (12, 25). Our data confirm a correlation between drug exposure (AUC) and hematologic toxicity. We showed a correlation between imatinib exposure (AUC) and a decrease in ANC (% ANC) and platelets (% platelets) over time. However, it was not a limiting factor leading to treatment discontinuation. Plasma AAG on day 1 was also correlated with a greater decrease in the ANC and platelets, indicating that patients with a high inflammatory response may be more vulnerable to toxicity, as already reported with other drugs (20).

Acquired resistance, as experienced in the treatment of chronic myeloid leukemia, is becoming a central issue in the treatment of advanced GIST with imatinib. Low drug exposure is one of the possible mechanisms of resistance to imatinib. Based on prior studies, the 400 mg daily dose was chosen for patients with advanced GIST, however, some patients might benefit from higher doses (14). The results of the crossover in the two phase III trials showed that after progression on 400 mg, 29% of patients may experience a clinical benefit with 800 mg (26, 27). We showed that the response rate was not correlated with imatinib exposure, as already reported by others (12). However, as the biological activity of imatinib is due to the free fraction, we explored the pharmacokinetics of both the total and the unbound fractions of imatinib, which was not done in the previous study. No relationship was observed between clinical activity and total or free unbound imatinib. The number of patients included in this trial may be too small for a difference to be identified between pharmacokinetics and such a multifactorial event, i.e., efficacy.

In conclusion, this study showed that the plasma AAG level seems to play a key role in the variability shown in imatinib pharmacokinetics and should certainly be taken into account when performing pharmacokinetic-pharmacodynamic exploration of imatinib therapy in patients with GIST.

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