Population Pharmacokinetics and Pharmacogenetics of Imatinib in Children and Adults

Aurélie Petain,1 Darouna Kattygnarath,4 Julie Azard,1 Etienne Chatelut,1 Catherine Delbaldo,2 Birgit Georger,2,3 Michel Barrois,4 Sophie Séronie -Vivien,1 Axel LeCesne,3 Gilles Vassal,2,3 and On behalf of the Innovative Therapies with Children with Cancer European consortium

Abstract

**Purpose:** The aim of this study was to explore the effect of several demographic, biological, and pharmacogenetic covariates on the disposition of imatinib and its main metabolite (CGP74588) in both adults and children.

**Experimental Design:** Thirty-three children with solid malignancies included in a phase II exploratory study and 34 adults with gastrointestinal stromal tumors received 340 mg/m² and 400 mg imatinib, respectively. Plasma imatinib and CGP74588 concentrations observed on day 1 and at steady-state were analyzed by a population pharmacokinetic method (NONMEM) to evaluate the effect of age, body weight, age, sex, albuminemia, plasma α1-acid glycoprotein (AGP), and eight polymorphisms corresponding to ABCB1, ABCG2, CYP3A4, CYP3A5, and AGP (pharmacogenetic data available for 46 of 67 patients).

**Results:** Analysis of the whole dataset in 67 patients showed that apparent clearance (CL/F) of imatinib was positively correlated with body weight and albuminemia and negatively with AGP. By considering these three covariates, the interindividual variability on CL/F decreased from 47% to 19%. The apparent clearance of CGP74588 was similarly dependent on both body weight and AGP and significantly lower (30% reduction) at steady-state. By adding genotype status to the final covariate imatinib model, a 22% reduction in CL/F was observed in heterozygous compared with wild-type patients corresponding to ABCG2 c.421C>A (P < 0.05).

**Conclusions:** By considering morphologic and biological covariates, a unique covariate model could be used to accurately describe imatinib pharmacokinetics in patients ages 2 to 84 years. Morphologic and biological characteristics have a stronger influence than pharmacogenetics on imatinib pharmacokinetics.

Imatinib mesylate (STI571, Glivec, Gleevec) is a highly selective inhibitor of Bcr-Abl, platelet-derived growth factor receptors, and c-KIT receptor tyrosine kinases (1, 2). It has significant activity in chronic myeloid leukemia and gastrointestinal stromal tumors (3, 4). Variation in drug disposition, especially plasma clearance (CL), may result in excessive toxicity or suboptimal anticancer efficacy. Trough imatinib plasma concentrations have been associated with complete cytogenetic and major molecular responses to a standard dose in chronic myeloid leukemia (5). The main toxicities of imatinib are frequently dose-related. Neutropenia has been correlated with the area under the curve of plasma imatinib concentrations (6). The standard dose used in adults is 400 mg/d, whereas children with Philadelphia chromosome-positive leukemia receive a standard daily dose of 340 mg/m².

Imatinib is well absorbed after oral administration with a bioavailability exceeding 90%. It is extensively metabolized by the hepatic cytochrome P450 enzyme system. There is evidence that CYP3A accounts for most of the metabolism of imatinib to the active metabolite CGP74588. Imatinib is also a substrate for the ABC transporters ABCB1 (P-glycoprotein) and ABCG2 (breast cancer resistance protein). Imatinib is extensively bound to plasma protein (free fraction ~ 4%) and mostly to α1-acid glycoprotein (AGP). Previous pharmacokinetic analyses showed that imatinib displayed linear pharmacokinetics (7).

Several clinical studies have been done to identify patients’ characteristics that could be linked to the interindividual variability of imatinib pharmacokinetics. Imatinib is insensitive to potent CYP3A4 inhibition (ritonavir coadministration; ref. 8) and the ABCB1 genotype was associated with steady-state imatinib clearance (9). By analyzing the pharmacokinetic data from 34 adult patients, we have shown previously that AGP levels influence the pharmacokinetics of both imatinib and CGP74588 (6). The objective of the present analysis was to combine these data with that obtained from children or young adult patients to evaluate the imatinib pharmacokinetics versus...
Translational Relevance

Biological, pharmacogenetic, and morphologic covariates have been identified to predict imatinib plasma exposure in both children and adults patients. That should help physicians to homogenize imatinib concentrations between adults and children. In the perspective of drug monitoring of imatinib, effect of α1-acid glycoprotein plasma levels on pharmacokinetic variables described in this article will allow to better interpret the observed imatinib concentrations. Pharmacokinetic-pharmacodynamic relationships will be better studied by considering this biological covariate. This work represents an additional work to quantify the effect of pharmacogenetics on tyrosine kinase inhibitors pharmacokinetics. In term of clinical methodology, this work should promote combined analysis of adults and children data during drug development of anticancer drugs.

A unique pharmacokinetic model to describe drug (and metabolite) plasma concentrations will allow to better identify pharmacodynamic characteristics in pediatrics (if any).

Materials and Methods

Patients

Adult patients (n = 34) with metastatic and/or unresectable malignant gastrointestinal stromal tumors were enrolled in the French Sarcoma Group, BFR 14 phase III trial. Study eligibility criteria have been described previously in detail (6). The main eligibility criteria were histologically documented diagnosis of advanced/metastatic gastrointestinal stromal tumors, immunohistochemically documented c-KIT (CD117) expression either in the primary tumor or in metastases determined using the DAKO assay, and age ≥18 years. The patients received imatinib (Glivec) 400 mg/d orally using the drug formulated as hard gelatin capsules. In cases where the disease progressed, the dose was increased to 600 mg/d. If progression was confirmed after 2 months of the increased dose, the treatment was stopped. The dose was decreased to 300 mg/d if grade 3 toxicity occurred. Children, adolescent, and young adult patients (ages <21 years; n = 33) with malignant solid tumors expressing at least one imatinib-sensitive tyrosine kinase receptor or in whom there was evidence of a potential pathogenic role of these tyrosine kinases were included within an open-label, exploratory phase II study (CST1 571BFR10) of the Innovative Therapies with Children with Cancer European consortium. Eligibility criteria included age between 6 months and 21 years; progressive malignant solid tumor, refractory or relapsing or for which no conventional therapy exists; nonmalignant diseases such as fibromatosis expressing c-KIT or platelet-derived growth factor receptor and for which a rationale for imatinib treatment exists; immunohistochemically positive KIT (CD117), platelet-derived growth factor receptor α or β in ≥80%; life expectancy >6 weeks; no concomitant anticancer or investigational drug; Karnofsky performance status or Lansky play score >50%; completion of anticancer therapy ≥4 weeks before study entry; adequate bone marrow reserve; aspartate aminotransferase/alanine aminotransferase ≤2.5 times the upper limit of normal (≤5 times the upper limit of normal if hepatic disease involvement); bilirubin ≤1.5 times the upper limit of normal; creatinine ≤1.5 times the upper limit of normal for age; no other serious concomitant illness; negative pregnancy test if appropriate; and use of adequate contraception. Glivec was administered orally to patients at an initial dose of 340 mg/m²/d. The dose was escalated up to 440 mg/m²/d if no significant improvement in the disease occurred after the first 4 to 8 weeks of therapy. For both children and adults, complete medical histories, a physical examination, and the following laboratory tests were done at baseline and at each scheduled visit: complete differential blood count, creatinine, serum electrolytes, calcium, uric acid, total protein, albumin, AGP, total bilirubin, alkaline phosphatase, glutamate pyruvate transaminase, glutamate oxaloacetate transaminase, γ-glutamyl transferase, lactate dehydrogenase, prothrombin time, activated partial thromboplastin time, and fibrinogen. Both studies were approved by independent institutional review board/ethical committees and conducted in compliance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice. Written informed consent was obtained from all subjects or parents in the case of minor. The patient characteristics are summarized in Table 1.

Table 1. Patient characteristics, mean (range)

<table>
<thead>
<tr>
<th></th>
<th>Children (n = 33)</th>
<th>Adults (n = 34)</th>
<th>All patients (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>13/20</td>
<td>6/28</td>
<td>19/48</td>
</tr>
<tr>
<td>Age (y)</td>
<td>(2-22)</td>
<td>(28-84)</td>
<td>(2-84)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>38 (12-80)</td>
<td>69 (45-100)</td>
<td>54 (12-100)</td>
</tr>
<tr>
<td>Albuminemia (g/L)</td>
<td>39 (27-47)</td>
<td>37 (23-46)</td>
<td>38 (23-47)</td>
</tr>
<tr>
<td>AGP plasma level (g/L)</td>
<td>1.10 (0.50-2.82)</td>
<td>1.13 (0.45-2.65)</td>
<td>1.13 (0.45-2.82)</td>
</tr>
</tbody>
</table>
respectively) was collected in heparinized tubes and centrifuged within 30 min at 4,000 × g for 15 min at 4°C, and 2.5 ml plasma was transferred into ice-cold propylene tubes and stored at -20°C until analysis.

Imatinib, CGP74588, and the internal standard (imatinib-D8) were provided by Novartis Pharma. Quantitative analyses of imatinib and CGP74588 were done using reverse-phase high-performance liquid chromatography with fluorescence detection and coupled with tandem mass spectrometry, as described previously (16), but using different instrumentation. Ten microliters of the standard, control, and patient samples were analyzed by the LC system [pump HP1100 model (Hewlett Packard Technology) and a detector quatto LC2 (Micromass)]. The analyses were done with the Masslynx program version 3.4 (6). The lower limit of quantification for both imatinib and CGP74588 was 10 ng/ml. For imatinib, the intra-day accuracy (% nominal) was between 97.8% and 107% and the precision (SD for replicate analysis) was from 2.3% to 10.4%. The inter-day accuracy was between 101% and 104% and the precision was from 4.3% to 7.1%. For CGP74588, the intra-day accuracy was between 85.5% and 100% and the precision was from 1.1% to 9.1%. The inter-day accuracy was between 87.4% and 95.8% and the precision was from 5.2% to 7.5%.

**Genetic analysis.** DNA was extracted from peripheral blood leukocytes according to standard procedures with QiAamp DNA Blood Mini Kit (Qiagen) according to the manufacturer’s instructions. Eight SNPs within the ABCB1, ABCG2, CYP3A4, CYP3A5, and AGP1 genes, most of them listed with theoretical minor allele frequencies superior to 5% in Caucasian population in the SNP official database (dbSNP, HapMap), were selected to be genotyped based on considerations provided by previous studies. SNPs in CYP3A4 [*1B (5'-LTR-392A>G; rs27405754), CYP3A5 [*1/*3 (c.219-237G>A; rs776746)], ABCB1 [c.1236T>C (rs1128503)] and c.3435C>T (rs1045642)] and ABCG2 [c.421C>A (rs2311142)] were genotyped using allelic discrimination with labeled probes (TaqMan): PCRs on DNA (20 ng final quantity) were carried out in a 10 μl reaction in a 96-well plate using TaqMan universal PCR master mix (Applied Biosystems) with forward and reverse primers (10 pmol for each primer) and FAM- and VIC-labeled probes (2 pmol for each probe) designed with OLIGO 6.0 software, except for ABCG2 were we used the TaqMan Drug Metabolizing Genotyping Assay (Assay-by-Design; Applied Biosystems) specific assay for SNP c.421C>A (reference ID C_15854163_70). Each sample was subjected to initial denaturation at 92°C for 10 min and then to the following 40 amplification cycles: 15 s at 92°C for denaturation and 1 min at 60°C for annealing. We read the completed PCRs on an ABI PRISM 7700 Sequence Detector in end-point mode using the Allelic Discrimination Sequence Detector Software 1.9.1 (Applied Biosystems). We duplicated each sample and included two nontemplate controls in each 96-well plate.

Other SNPs in ABCB1 [c.2677G>T/A (rs203258)] and AGP1 [c.190A>G and c.3520G>A] were genotyped by direct sequencing. Briefly, PCR for ABCB1 was carried out in a total reaction volume of 10 μl containing 20 ng total DNA, 10 pmol of each primer, 200 μmol/L deoxynucleotidetriphosphates, 1.5 mmol/L MgCl2, and 0.2 units Hot Start Taq polymerase Qiagen over 40 cycles (initial denaturation at 95°C for 10 min and then 40 amplification cycles: 30 s at 95°C for denaturation, 1 min at 60°C for annealing, and 1 min at 72°C for extension). Amplification for AGP1 was done according to protocol published by Yuasa et al. (17). PCR products were first purified using ExoSAP-IT PCR purification kit (USB) and sequenced with the Big Dye Terminator v.3.1 kit (Applied Biosystems). Sequencing was done on an ABI3730 automatic DNA sequencer (Applied Biosystems) on 96-well plates. Genotypes were identified by visual inspection of the sequence with Seqscape software (Applied Biosystems).

**Population pharmacokinetic analysis.** Plasma imatinib and CGP74588 concentrations were analyzed according to a nonlinear mixed effects ("population") approach using the NONMEM program (version VI, level 1; Icon Development Solutions) running on a PC (Pentium 200 pro) using the first order conditional estimation method. A proportional error model was used for both interpatient and residual variability. The influence of the seven following covariates on pharmacokinetic variables was examined: age, sex, body weight, albuminemia, plasma AGP level, occasion (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), and study (0 for adults and 1 for children). For biological covariates (e.g., AGP), the specific value at each stage of the pharmacokinetics study (day 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 body weight, for example, \( CL = 01 \) (body weight / mean body weight)\(^{\text{92}}\), where 01 is the typical value of CL for a patient with the mean covariate and 02 is the estimated influential factor for body weight. Full and reduced models (one variable less) were compared by the \( \chi^2 \) test of the difference between their respective objective function values (OBV). The OBV 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 decrease of at least 3.84 (\( P < 0.05, 1 \text{ df} \)) 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. Covariates remained in the final population pharmacokinetic model when the removal of the covariate resulted in an increase of at least 10.83 (\( P < 0.001, 1 \text{ df} \)). 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 the covariates on imatinib variables) were fixed while developing the CGP74588 pharmacokinetic model. A bioavailability score (F) of 1 was assumed in the absence of i.v. drug administration data.

Pharmacogenetic data were available for 46 of 67 patients (16 adults and 30 children or young adults): ABCB1 [c.1236T>C, c.2677G>T/A, and c.3435C>T], ABCG2 [c.421C>A, CYP3A4 [*1B (5'-LTR-392A>G), CYP3A5 (c.219-237G>A), and AGP1 (c.190A>G and c.3520G>A)]. Each of these polymorphisms was tested by adding a genetic factor to the final covariate model previously obtained for imatinib and CGP74588 clearance.

**Results**

**Pharmacokinetics model and morphologic and biological covariates.** A total of 558 plasma samples were available, but only 505 (200 from adults and 305 from children) were taken into account for the population pharmacokinetic analysis. To identify unexpected low values, a preliminary analysis based only on the imatinib data obtained after the first administration (day 1) was done. Observed concentrations at days 30 and 60 were compared with the corresponding levels predicted according to the individual day 1 pharmacokinetic variables obtained by this preliminary analysis. Observed concentrations lower than 20% of the predicted values were excluded. For most of these 53 concentrations, poor compliance was confirmed by the patients or interviews with parents.

The pharmacokinetics was adequately described by a onecompartment model with a first-order absorption and first-order elimination. The corresponding pharmacokinetic variables were \( K_{a} \) (absorption rate constant), \( V \) (volume of distribution of imatinib), and CL (total plasma clearance of imatinib). The basic pharmacokinetic model included interoccasion variability of \( V \).

During the individual testing of the 7 covariates, 5 covariates (study, body weight, age, AGP, and albuminemia) were...
significantly \( P < 0.05\) correlated with CL and/or V. A stepwise backward elimination applied to the intermediate model identified the following as significant \( P < 0.001\) covariates: body weight, AGP, and albuminemia for CL (positively correlated with body weight and albuminemia and negatively with AGP), body weight, and AGP for V (positively correlated with body weight and negatively with AGP). The final covariate models are detailed in Table 2. The interindividual variability in CL, expressed by the coefficient of variation, decreased from 47\% (no covariate) to 19\% when body weight, AGP, and albuminemia were all taken into account together. For V, the interindividual variability was 63\% for the model without covariates and not assessable when body weight and AGP were taken into account. However, substantial interoccasion variability (60\%) was observed for V. Residual variability was 33.6\% for imatinib concentrations.

Analysis of both plasma imatinib and CGP74588 concentrations required an additional compartment and the corresponding variables: Vm/fm (apparent volume of distribution of CGP74588) and CLm/fm (apparent total clearance of CGP74588), where fm is the fraction of imatinib converted into CGP74588. Residual variability was 34.8\% for CGP74588 concentrations. Three covariates (body weight, AGP, and occasion) were significantly \( P < 0.05\) correlated with CLm/fm. All these three covariates remained significant after a stepwise backward elimination procedure from the intermediate model (Table 2). CLm/fm was positively correlated with CLm/fm. After a stepwise backward elimination procedure from the intermediate model (based on body weight, AGP plasma levels, and albuminemia) versus actual clearance (corresponding to post hoc values of the run without covariates).

The model adequately described imatinib and CGP74588 pharmacokinetic profiles (Figs. 1 and 2). Figure 3 shows the predicted imatinib clearance corresponding to the final covariate model (based on body weight, AGP plasma levels, and albuminemia) versus actual clearance (corresponding to the post hoc values of the run without covariates).

**Pharmacogenetics.** The patient’s distributions for each polymorphism are shown in Table 3. Each variant genotype (GEN)
was tested by inclusion of a factor (\(u_5\)) within the final model previously obtained according to the following equation:

\[
CL = u_1 \left(\frac{\text{body weight}}{54}\right) u_2 \left(\frac{\text{AGP}}{1.13}\right) u_3 \left(\frac{\text{albuminemia}}{38}\right) u_4 u_5 \text{GEN},
\]

where \(\text{GEN} = 0\) for homozygous wild-type patients and 1 for heterozygous or homozygous variant-type patients. Only \(\text{ABCG2}\) polymorphism was associated with a significant decrease of the OBV (-6.1; \(P < 0.05\)) with a 95\% confidence interval of 0.77 ± 0.28 corresponding to a 23\% lower imatinib CL in heterozygous versus homozygous wild-type patients. Only \(\text{ABCG2}\) polymorphism was associated with a significant decrease of the OBV. A similar evaluation (individual test of the genotype within the final covariates model) was conducted for variant genotypes and CGP74588 apparent clearance (CLm/fm). No polymorphism was associated with a significant decrease of the OBV.

### Discussion

Population pharmacokinetic analyses tend to be conducted systematically for new anticancer drugs to identify the patients’ covariates that correlate with pharmacokinetic variables. However, only a few studies have been published from a database combining children and adults data (18). This is of major importance because extrapolation from adult pharmacokinetic data to the pediatric population is of increasing interest when defining the optimal dose of an anticancer drug in children. Indeed, for targeted compounds whose antitumor activity is observed at an optimal biological dose rather than a maximum tolerated dose, pharmacokinetic extrapolation from adults to children may avoid lengthy dose-escalating trials in the pediatric population. Imatinib is a good example of this new situation in the field of anticancer drug development. Indeed, no maximum tolerated dose was found either in adults (19) or in children, whereas a classic dose-escalation trial using the 3 × 3 design was done in children (20). The goal of the present study was to retrospectively analyze two sets of pharmacokinetic data, one from adults and the other one from children, to answer the question: Does imatinib disposition differ between adults and children?

### Table 3. Primers, labeled probes, and frequencies for variant genes studied: number of patients (children/adults)

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Primers and probes for TaqMan assay or sequencing</th>
<th>Sequence (5‘-3’)</th>
<th>Homozygous wild</th>
<th>Heterozygous</th>
<th>Homozygous mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{ABCB1})</td>
<td>c.2677G&gt;T/A</td>
<td>(\text{ABCB1}<em>2677</em>\text{F}) (\text{ABCB1}<em>2677</em>\text{R})</td>
<td>TAGGTTCCAGGCTTGCTGTA TCAAGAAGCTGCTTTGC</td>
<td>14 (9/5)</td>
<td>26 (17/9)</td>
<td>6 (4/2)</td>
</tr>
<tr>
<td>(\text{ABCB1})</td>
<td>c.1236T&gt;C</td>
<td>(\text{ABCB1}<em>1236</em>\text{T FAM-MGB}) (\text{ABCB1}<em>1236</em>\text{C VIC-MGB})</td>
<td>TCAAGGTTAGGAGGCTTTC</td>
<td>11 (6/5)</td>
<td>26 (16/10)</td>
<td>9 (8/1)</td>
</tr>
<tr>
<td>(\text{ABCB1})</td>
<td>c.3435C&gt;T</td>
<td>(\text{ABCB1}<em>3435</em>\text{T FAM-MGB}) (\text{ABCB1}<em>3435</em>\text{C VIC-MGB})</td>
<td>TCTTATATCTTGTGGTAAGTGG GCCTTTCCTACACGACACGT</td>
<td>14 (7/7)</td>
<td>24 (18/6)</td>
<td>8 (5/3)</td>
</tr>
<tr>
<td>(\text{ABCG2})</td>
<td>c.421C&gt;A</td>
<td>TaqMan drug-metabolizing genotyping assay (\text{Applied Biosystems (reference ID C_15854163_70)}) primers and probes available with manufacturer</td>
<td>ACGTGGAACTTGGAACTGGA</td>
<td>41 (27/14)</td>
<td>5 (3/2)</td>
<td>0</td>
</tr>
<tr>
<td>(\text{CYP3A4})</td>
<td>5’-UTR -392A&gt;G</td>
<td>(\text{CYP3A4<em>_1B-G FAM-MGB}) (\text{CYP3A4</em>_1B F}) (\text{CYP3A4*_1B R})</td>
<td>ACAAGGCGACGGAGC</td>
<td>42 (26/16)</td>
<td>3 (3/0)</td>
<td>1 (1/0)</td>
</tr>
<tr>
<td>(\text{CYP3A5})</td>
<td>c.219-237G&gt;A</td>
<td>(\text{CYP3A5<em>_3-A FAM-MGB}) (\text{CYP3A5</em>_3-A FAM-MGB})</td>
<td>CAGGGCGGACGAGG</td>
<td>36 (22/14)</td>
<td>8 (6/2)</td>
<td>2 (2/0)</td>
</tr>
<tr>
<td>(\text{AGP1})</td>
<td>c.190A&gt;G</td>
<td>(\text{AGP1}<em>190</em>\text{F}) (\text{AGP1}<em>190</em>\text{R})</td>
<td>ACCTGCTGTTGTCTTGAATCG</td>
<td>F1F1: 24 (16/8)</td>
<td>F1F2: 2 (1/1)</td>
<td></td>
</tr>
<tr>
<td>(\text{AGP1})</td>
<td>c.520G&gt;A</td>
<td>(\text{AGP1}<em>520</em>\text{F}) (\text{AGP1}<em>520</em>\text{R})</td>
<td>TTTTGGTGTCGTCG</td>
<td>F1S: 10 (7/3)</td>
<td>SS: 10 (7/3)</td>
<td></td>
</tr>
</tbody>
</table>

*Correspondence between amino acid composition and \(\text{AGP1}\) variants: F1, Gin38-Val174; F2, Gin38-Met174; S, Arg38-Met174. \(\text{AGP1}\) was genotyped according to Yuasa et al. (17).
By simultaneously analyzing the data from 2- to 84-year-old patients, we have been able to obtain a structural model that provided a good fit to the data. This model was based on a first-order absorption as used by van Erp et al. for a population analysis of rich data (9 blood samples per patient) for an imatinib pharmacokinetic study (8). The mean predicted concentrations (Fig. 2) were lower in adults than in children due to both a slightly higher mean dose in children (417 versus 400 mg in adults) and lower mean clearance in children (6.20 versus 8.22 L/h in adults). A common covariates model based on bodyweight, AGP, and albuminemia enabled more than the half of the interpatient variability in imatinib CL to be explained (from 47% to 19%; Table 2). By considering these covariates, the covariate study (initially significant when tested alone) became nonsignificant showing the homogeneity of the covariates pharmacokinetic model between children and adults and the lack of age-dependency. Correlation between CL and body weight was expected considering the large range of the patients’ morphology (Table 1). AGP was confirmed as a significant covariate for both imatinib and CGP74588 clearance. The higher the AGP level, the lower is the plasma unbound fraction of these two compounds and thus the lower is their liver clearance. The need to consider the plasma protein binding when exploring the correlations between pharmacokinetics and pharmacodynamics of imatinib is reemphasized by these results. A positive and slight correlation was observed between imatinib CL and albuminemia: hypoalbuminemia is one of the criteria of Child-Pugh classification for liver function. The population pharmacokinetics of imatinib in children and young adults have been recently reported by Menon-Andersen et al. (21): body weight was the only covariate found to significantly affect imatinib CL decreasing its interindividual variability from 52% (no covariate) to 31.7%, but AGP was not evaluated. Overall, the results of the two studies are very consistent because we found an interindividual variability of 47% (no covariate) decreasing to 29% by considering both body weight and albuminemia (mainly due to body weight because albumin affected the OBV but not the interindividual variability). Moreover, the mean imatinib clearance was 6.81 (21) versus 6.20 L/h for the children or young adults in our study.

As shown previously for adults (6), a significant decrease in apparent plasma clearance of the metabolite (CLm/fm) was observed over time, with a lower value (30% decrease) at steady-state than that observed on day 1. Analysis of only the data from the children confirmed this phenomenon with a typical value of CLm/fm at steady-state representing 72% of that at day 1 (data not shown). This may correspond to either a decrease in the elimination of CGP74588 (CLm) or an increase in the fraction of imatinib converted into CGP74588 (fm).
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 (V_m/f_m) and a change in imatinib clearance (CL). Such changes were not observed. The first hypothesis may correspond to saturation of the metabolism of CGP74588 when its concentration reaches a higher level due to an accumulation process. This hypothesis would be consistent with the results of a study done by van Erp et al. with the objective of evaluating the effect of ritonavir (as a potential CYP3A4 inhibitor) on imatinib pharmacokinetics (8). They observed that the metabolism of CGP74588 was decreased by ritonavir but not that of imatinib. The results suggest that CGP74588 metabolism would be more dependent on the plasma concentration and interaction than imatinib.

Several studies have explored the effect of the pharmacogenetics of several ABC transporters (ABCB1 and ABCG2) and cytochrome P450 enzymes on imatinib disposition. No significant link between common genetic variants and the pharmacokinetics of imatinib was observed by Gardner et al. (22). Gurney et al. (9) only observed a correlation between the ABCB1 genotype and the change in imatinib apparent clearance (CL/F) between day 1 and steady-state. The reduction in CL/F was least apparent in thymidine homozygotes such as the c.1236T>C, c.2677G>T/A, and c.3435C>T. However, they did not observe any correlation between ABCB1 genotype and values of CL/F. By evaluating the effect of each of the common

Fig. 3. Predicted imatinib clearance corresponding to the final covariate model (based on body weight, AGP plasma level, and albuminemia) versus actual clearance.

Fig. 2. Imatinib (A) and CGP74588 (B) observed and predicted plasma concentrations versus time profiles.
genetic variants of ABCB1, ABCG2, CYP3A4, CYP3A5, and AGP on typical values of imatinib clearance based on morphologic (body weight) and biological (albuminemia and AGP) covariates, we observed a significantly lower clearance in heterozygous versus wild-type homozygous patients for ABCG2 c.421C>A (-23%; P < 0.05). It is noteworthy that inclusion of this polymorphism alone on typical values of imatinib clearance (model without any morphologic or biological covariates) was not associated with a significant decrease of the objective function (data not shown). Overall, the previously published and the present pharmacogenetic results are consistent; the common genetic variants only have a limited effect on imatinib pharmacokinetics. The ABCG2 c.421C>A genotype seems to be more relevant than the others as it has been shown for topoisomerase I inhibitors (23, 24). This clinical result is in accordance with cellular studies showing that imatinib has a high-affinity interaction with ABCG2 on primitive hematopoietic stem cells (25).

In conclusion, morphologic and biological characteristics allowed us to explain around half of the pharmacokinetic variability for imatinib and its active metabolite and that pharmacogenetics has a modest effect. The only way to perfectly control the imatinib concentrations would be based on therapeutic drug monitoring as has been proposed for the management of chronic myeloid leukemia. Indeed, Picard et al. (5) showed that mean trough plasma concentrations of imatinib were significantly lower in patients without a complete cytogenetic response. Again, we suggest considering the protein-binding phenomenon and its interindividual variability corresponding to AGP levels when exploring the pharmacokinetic-pharmacodynamic relationships for this drug. Finally, the lack of difference in imatinib disposition between adults and children argues for other designs for defining the dose in the pediatric population than the classic 3 × 3 dose escalation phase I studies, when the drug being studied is active at an optimal biological dose rather that at its maximum tolerated dose.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Micheline Re for the analysis of the pharmacokinetic samples, all the patients and parents who participated in the trials, the clinical teams of the centers (Institut Gustave Roussy, Institut Curie, Centre Oscar-Lambret, Centre Leon-Berard, Hôpital Trousseau, CHU La Timone, CHU Toulouse, Royal Marsden, Royal Infirmary, and AMC), and John Woodley for editorial assistance with the English.

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