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ORIGINAL RESEARCH

Personalized Dose of Adjuvant Imatinib in Patients with Gastrointestinal Stromal Tumors: Results from a Population Pharmacokinetic Analysis

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Purpose: Imatinib is the first-line treatment for patients with gastrointestinal stromal tumors (GIST) after surgery. However, its pharmacokinetic profile varies remarkably between individuals and has not been well characterized in postoperative Chinese patients with GIST. Therefore, this study aimed to develop a population pharmacokinetic (PPK) model and recommend appropriate doses for different patients to achieve the target trough concentration in such a population.

Patients and Methods: A total of 110 surgically treated GIST patients were enrolled, of which 85 were applied to conduct a PPK analysis with a nonlinear mixed-effect model and 25 for external validation of the model. Demographic and biomedical covariates, as well as six single nucleotide polymorphisms were tested to explore the sources of variation in pharmacokinetic parameters of imatinib. Monte Carlo simulations were performed to establish the initial dosing regimens.

Results: A one-compartment model was established in postoperative GIST patients. The red blood cell count (RBC) and *ABCG2* rs2231142 were observed to have a significant effect on the clearance of imatinib. The typical values estimated by the final model were 9.72 L/h for clearance (CL/F) and 229 L for volume of distribution (V/F). Different from the fixed dose regimen of 400 mg each day, patients carrying rs2231142 heterozygous type and with a lower level of RBC (2.9×10^{12}/L), 300 mg imatinib daily is enough to achieve the target trough concentration. When RBC rises to 4.9×10^{12}/L, 500 mg daily is recommended. For patients with rs2231142 GG genotype, 500 mg a day is required at RBCs of 3.9×10^{12}/L and 4.9×10^{12}/L.

Conclusion: RBC and rs2231142 contribute to the pharmacokinetic variation of imatinib and personalized dose recommendations based on patient characteristics may be necessary.

Keywords: imatinib, PPK, rs2231142, RBC, personalized dose, GIST, postoperative

Introduction

Gastrointestinal stromal tumors (GISTs) are the most usual type of mesenchymal tumors with an annual incidence of approximately 1.2/100,000 in most countries.[1] Before 2002, surgical resection was the only treatment for GIST, but even though complete resection was achieved, the five-year survival rate was only 54%.[2] Imatinib, approved in 2002, is a recognized standard treatment for GIST and chronic myeloid leukemia (CML) and provides a significant survival benefit to patients with these malignancies. Adjuvant treatment with imatinib improves survival in imatinib-sensitive patients with *KIT* or *PDGFRA* mutations. The combination of imatinib with surgery was found to increase the 5-year survival rate to around 80% and significantly improve patient prognosis.[1,3]

Imatinib is characterized by substantial inter-individual variability in pharmacokinetic characteristics (range, 38–75%), and its clinical efficacy is difficult to observe.[4] However, significant relationships exist between the concentration and efficacy of imatinib and it shows concentration-dependent inhibition against PDGFRA and c-KIT.[5] The success of

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imatinib is largely associated with its favorable pharmacokinetic profile, and the absolute bioavailability of oral imatinib is 98.3%, indicating nearly complete absorption.[6] However, imatinib shows a decreasing trend in bioavailability after repeated dosing, and one month after the first dose, the bioavailability of imatinib decreases by about 17%.[7] Imatinib binds approximately 95% to plasma proteins, mainly plasma albumin, followed by alpha-acidic glycoprotein; a small fraction binds to lipoproteins. A critical factor in the success of drugs lays in the uptake of the drugs by cells. Imatinib acts as a substrate for influx transporter OCT1 and efflux transporter ABCG2. Other transporters, including the family of organic anion transporters, such as OATP1A2, are also involved in the transport process of imatinib. The genes encoding them are highly polymorphic,[8,9] which may facilitate the variability in pharmacokinetics of imatinib. Imatinib is metabolized to its active metabolite, CGP74588, in the liver. CGP74588 also exerts antitumor effects with a half-life of 40–60 hours, which is significantly longer than the 18–20-hour half-life of imatinib and its area under the curve is approximately 16% of that of imatinib.[10–12] Compared to a Western population, Chinese patients with GIST experience higher imatinib exposure under the same dose of imatinib, especially at higher doses. Therefore, Chinese populations are more likely to experience adverse effects such as edema, anemia, and gastrointestinal reactions than Western populations, resulting in a lower tolerable dose of imatinib in the Chinese population.[13] As a result, a separate analysis conducted in Chinese patients with GIST is necessary.

Population pharmacokinetics (PPK) integrate the basic principles of classical pharmacokinetics with statistical methods oriented to study the population patterns of drug processes in vivo. This method allows for quantitative analysis of the connections between variability in pharmacokinetic parameters and underlying factors in a specific population and accurate estimation for individual pharmacokinetic parameters with different calculation methods.[14]

Currently, imatinib is usually administered orally at a fixed dose of 400 mg/d in clinical practice. However, there are data suggesting that only about 40% of patients achieve the effective concentration threshold 1100 ng/mL using this fixed dose regimen,[15,16] which leads to significant interpatient differences in prognosis and adverse reactions.[17] There is growing voice in favor of personalized dose of imatinib,[4,18,19] and the goal of this research was to development a PPK model to study the effects of various covariates on the pharmacokinetic profile of imatinib and generate dosage recommendations based on the findings for such a population.

Materials and Methods

Patients

From March 2021 to June 2022, surgery-treated GIST patients, receiving imatinib (range, 200–600 mg daily), were included. Patients who (1) with GIST that has been confirmed by histology; (2) age ≥ 18 years at surgery; and (3) at intermediate or high risk of recurrence as defined by the modified National Institutes of Health (NIH) criteria and had been taking imatinib regularly were eligible.[20] Patients who (1) were lost to follow-up; and (2) with inadequate available data (more than 10% of the required information is missing) were excluded from this study.

The present research was granted by the medical ethics review board of the First Affiliated Hospital of Nanchang University (Medical Ethics No. 12-001). The included patients all agreed to participate and were followed up regularly. Electronic medical and patient medical records were used to track demographic information and laboratory data of patients.

Concentration Monitoring

Most blood samples were obtained from patients under steady state (treatment with imatinib for at least 30 days). The samples were first deproteinated, followed by centrifugation, and the supernatant was applied for quantitation of imatinib concentration through two-dimensional liquid chromatography.[21] Samples were preliminarily extracted and separated on the one-dimensional chromatographic column (Aston SX1, 3.5 mm × 25 mm, 5 μm) and then transferred from the one-dimensional chromatographic column to the two-dimensional chromatographic column (Aston SCB, 4.6 mm × 125 mm, 5 μm) through the intermediate column (Aston SCB, 4.6 mm × 10 mm, 3.5 μm) for secondary separation, followed by analysis. All three columns were placed in the same column oven with a temperature of 40°C and injection volume of 500 uL. The standard curve has a linear range of 13.44–1400.00 ng/mL, and the quantification has a lower limit of 6.72 ng/mL.

The relative standard deviations of inter- and intra-day for concentrations of 33.60, 896.00, and 1120.00 ng/mL were 0.3–4.0% and 1.1–3.2%, respectively.

Genotyping Analysis

DNA was obtained from blood samples with DNA extraction kit (Tiangen Biotechnology, Beijing, China) and then placed at −20°C. Genotyping procedures were performed with the MassARRAY technology, which involves single base extension assays and multiplex polymerase chain reaction. Patients were genotyped for rs11636419 in *CYP1A2*; rs1867351, rs683369, and rs2282143 in *SLC22A1*; rs10841803 in *SLCO1A2*; and rs2231142 in *ABCG2*. For the Chinese population, the minor allele frequencies of the above single nucleotide polymorphisms (SNPs) were at least 0.1.

The Chi-squared test was used to determine whether these SNPs met Hardy–Weinberg equilibrium (HWE), and the SHEsisPlus tool was applied to assess the linkage disequilibrium (LD) of studied SNPs.[22]

PPK Analysis

The PPK analysis was developed with NONMEM (version 7.3, ICON Development Solutions, MD, USA). Results output and model evaluation were performed with R (version 4.0.5). To estimate the PPK parameters, a first-order conditional estimation method including interaction of intra- and inter-individual variabilities was adopted in the modeling.

Base Model

Imatinib is best characterized by a one-compartment model with first-order absorption and elimination according to previous studies,[23–25] and the absorption rate constant (k_a) was fixed to 1.22 h^{-1}.[26] Inter-individual variation was characterized by the exponential model (Equation 1):

$$P_i = TV(P) \times \exp(\eta_i) \quad (1)$$

where P_i is the parameter value considering inter-individual variation and TV (P) is defined as the parameter typical value. Inter-individual random variation is represented by η_i, which follows a Gaussian distribution with a variance of ω^2.

Error models of additive (Equation 2), proportional (Equation 3) and combined (additive and proportional, Equation 4) were applied to evaluate residual unexplained variability.

$$Y = F + \varepsilon_1 \quad (2)$$

$$Y = F \times (1 + \varepsilon_1) \quad (3)$$

$$Y = F \times (1 + \varepsilon_1) + \varepsilon_2) \quad (4)$$

where Y is defined as the observation and F is the corresponding prediction. Moreover, ε_1 and ε_2 represent residual variations, which obey a Gaussian distribution with a variance of ${\sigma_1}^2$ and ${\sigma_2}^2$, respectively.

Covariate Model

To explore the sources of variation in pharmacokinetic parameters, as well as to improve the predictive ability of the final model, a covariate model was established. The effects of demographics, laboratory data, and genetic factors on the model parameters were investigated. The investigated categorical covariates included sex and genetic polymorphisms of *CYP1A2* (rs11636419), *SLC22A1* (rs1867351, rs683369, and rs2282143), *SLCO1A2* (rs10841803), and *ABCG2* (rs2231142). Continuous covariates considered were age, body weight (WT), red blood cell count (RBC), hemoglobin (HGB), white blood cell count (WBC), platelet count (PLT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), globulin (GLB), albumin (ALB), and creatinine clearance rate (CRCL). The correlations of these covariates were analyzed prior to establishing the covariate model. An absolute value of the correlation coefficient ≥0.5 was considered significant. Of the two correlated covariates, only one was included to avoid collinearity and instability of the parameter estimates.

For the selection process of potential covariates, a stepwise method was implemented and it works based on the change of the objective function value (OFV), which is a measure of the fit of the model and changed after the inclusion of covariates. ΔOFV is approximate to a χ^2 distribution when there are nested relationships between models. In the process of forward inclusion, a covariate was considered to be included when the decrease of OFV more than 3.84 (df = 1, $p < 0.05$). In the backward elimination process, a covariate was retained when the increase of OFV > 6.63 (df = 1, $p < 0.01$), otherwise it was eliminated. Linear (Equation 5), exponential (Equation 6), or power function (Equation 7) models was applied to assess the roles of continuous covariates for pharmacokinetic parameters.

$$P = TV(P) + \theta * (Cov/Ref) \tag{5}$$

$$P = TV(P) \times \exp(\theta * Cov/Ref) \tag{6}$$

$$P = TV(P) \times (Cov/Ref)^{\theta} \tag{7}$$

where P represents the individual value of parameters, TV (P) is the typical value, and θ is the covariate coefficient. Moreover, Cov represents the corresponding covariate value, and Ref represents the median of the covariate values.

Equation 8 was applied to test the effects of categorical covariates (such as the genetic polymorphisms) on pharmacokinetic parameters, which were evaluated as a separate fixed effect.

$$P = TV(P) * \theta_1^{\text{heterozygous}} * \theta_2^{\text{homozygous}} \tag{8}$$

where TV (P) is defined as the typical value of the wild type, θ_1 is defined as the coefficient of the heterozygous type, and θ_2 is the coefficient of the homozygous mutations.

Model Evaluation

The degree-of-fit of the model was judged by the goodness-of-fit and diagnostic plots. The bootstrap method was utilized to verify the robustness and reliability of the model,[27] which involves resampling to generate 1000 datasets from the original dataset, calculating parameters for each of the datasets, and finally summarizing parameter estimates. The prediction- and variability-corrected visual predictive check (pvcVPC, n = 1000) was chosen to test the predictability of the model,[28] which relies on graphical presentation of a match between the simulated values and the observed values. Furthermore, the final model was validated using a new dataset (data from another 25 patients) other than the modeling data. Mean prediction error (MPE) and mean absolute prediction error (MAPE) were adopted as evaluation indicators, and the MPE% and MAPE% based on the population predictions were considered acceptable when they were ≤ ± 20% and ≤30%, respectively.

Dosage Simulation

Based on the final model, the Monte Carlo simulations (n = 1000) were used to predict the trough concentrations after 30-day imatinib treatment in different dosing regimens (200–600 mg daily) and generate the dosing recommendations for different patients to reach the therapeutic concentration threshold (1100 ng/mL).

Results

Patient Characteristics

During the modeling, 85 postoperative GIST patients, including 46 males and 39 females, were included, and the mean weight of patients was 58.6 ± 9.6 kg (range, 40.0–82.5 kg). Additional 25 patients were enrolled for external validation of the final model. The majority of patients were given 400 mg of imatinib once a day, with a range of 200–600 mg. Table 1 shows the characteristics of patients.

The frequencies and distributions of the six SNPs, as well as the p-values for the HWE are displayed in Table 2. All SNPs satisfied the HWE ($p > 0.05$), and none of them were in LD (Supplementary Figure 1).

Table 1 Patient Characteristics

Characteristics	Modeling Dataset	Validation Dataset
Number of patients	85	25
Male/female	46/39	14/11
Age (year)	57 (27–79)	58 (27–79)
Body weight (kg)	58.6 ± 9.6 (40.0–82.5)	60.7 ± 10.2 (45.0–86.0)
Initial dose (200/300/400/500/600 mg)	1/2/79/2/1	0/0/22/0/3
White blood cell count (10^9/L)	4.0 (1.4–20.9)	5.0 ± 1.5 (2.8–8.6)
Red blood cell count (10^{12}/L)	3.7 ± 0.6 (2.2–5.6)	3.8 ± 0.5 (3.1–5.0)
Platelet count (10^9/L)	178.0 (54.0–512.0)	191.9 ± 49.4 (71.0–296.0)
Hemoglobin (g/L)	115.9 ± 15.8 (71.0–156.0)	117.8 ± 15.4 (92.0–152.0)
Albumin (g/L)	44.0 (30.6–54.8)	43.9 ± 3.3 (38.4–50.2)
Globulin (g/L)	23.9 ± 4.2 (12.6–37.8)	24.8 ± 5.1 (14.0–33.1)
Alanine aminotransferase (U/L)	16.9 (2.0–645.0)	16.7 (13.9–34.7)
Aspartate aminotransferase (U/L)	23.9 (11.0–724.8)	22.2 ± 4.3 (15.0–29.5)
Creatinine clearance rate (mL/min)	69.7 (28.5–118.8)	77.2 (32.5–143.0)

Notes: Normally distributed data was expressed as mean ± SD (range); non-normally distributed data was expressed as medium (range).

Table 2 Genotype Frequencies and Hardy-Weinberg Equilibrium

Gene	SNP	Genotype	N	Identified Frequency	Allele	Allele Frequency	χ^2	HWE *P*
CYP1A2	rs11636419	GG	6	0.07	G	0.21	2.02	0.36
		GA	24	0.28	A	0.79		
		AA	55	0.65				
SLC22A1	rs1867351	CC	13	0.15	C	0.39	0.01	1.00
		CT	40	0.47	T	0.61		
		TT	32	0.38				
	rs683369	CC	65	0.76	C	0.88	0.09	0.96
		CG	19	0.22	G	0.12		
		GG	1	0.01				
	rs2282143	CC	62	0.73	C	0.86	0.39	0.82
		CT	22	0.26	T	0.14		
		TT	1	0.01				
SLCO1A2	rs10841803	GG	29	0.34	G	0.59	0.20	0.90
		GA	43	0.51	A	0.41		
		AA	13	0.15				
ABCG2	rs2231142	GG	34	0.40	G	0.66	2.99	0.22
		GT	45	0.53	T	0.34		
		TT	6	0.07				

PPK Analysis

The collected data of 85 patients were well described by a one-compartment model (subroutine ADVAN2 and TRANS2) with first-order absorption and elimination. An exponential model and a proportional error model were utilized to characterize the inter-individual variation on the clearance and residual variation, respectively. The estimated typical value of apparent clearance (CL/F) was 9.72 L/h, and apparent volume of distribution (V/F) was 229 L. The inter-individual variation on CL/F and the proportional residual error was found to be 13.9% and 29.6%, respectively. Inter-individual variation on V/F was not estimated in this analysis because only trough concentrations were collected and the estimate of inter-individual variation in the distribution volume was <1%. The estimated results are shown in Table 3.

Table 3 Population Pharmacokinetic Parameter Estimates and Bootstrap Results of the Final Model

Parameter	Estimates	RSE (%)	Bootstrap
			Median (95% CI)
Ka (1/h)	1.22 (Fixed)	–	–
CL/F (L/h)	9.72	8	9.72 (8.22–11.84)
V/F (L)	229	21	226.3 (156.4–421.6)
RBC	0.49	38	0.48 (0.10–0.89)
rs2231142 GG	1 (Fixed)	–	–
rs2231142 GT	0.879	5	0.877 (0.785–0.968)
rs2231142 TT	0.976	9	0.976 (0.801–1.582)
Inter-individual variation			
CL/F	0.139	39	0.133 (0.061–0.197)
Residual			
Proportional	0.296	27	0.288 (0.219–0.371)

Abbreviation: RSE, residual standard error.

Covariate Modeling

After the correlation analysis (Supplementary Figure 2), demographic and biochemical covariates including WT, WBC, RBC, PLT, ALB, GLB, ALT, and CRCL as well as six SNPs were introduced into the modeling process. RBC, CRCL, and rs2231142 were revealed to exert a notable effect on CL/F of imatinib in the univariate process of forward inclusion. However, the influence of CRCL on CL/F was not considerable during a multifactorial analysis ($\Delta OFV < 3.84$). Therefore, only two covariates were screened in the backward elimination process, and both showed a stable influence on the imatinib CL/F ($\Delta OFV > 6.63$). Eventually, RBC and rs2231142 were adopted into the model. The covariates that showed a remarkable influence on the CL/F of imatinib during the stepwise process are displayed in Table 4, and the formula of the final model was expressed as:

$$CL/F(L/h) = 9.72 \times (RBC/3.7)^{0.49} \times 0.879^{\text{heterozygous}} \times 0.976^{\text{homozygous}} \times e^{0.0192}$$

$$V/F(L) = 229$$

where the corresponding index is one or zero depending on the genotype of rs2231142, and both are zero when rs2231142 is GG.

Model Evaluation

The final model with covariates provides a good description of the population data, and the majority of the CWRES are symmetrically distributed (within ± 2) on each side of the line (y = 0), which indicates that the final model fits well, as shown in Figure 1. In the bootstrap, the model succeeded 990 times in 1000 datasets, indicating that the model robustness

Table 4 Significant Covariates in the Stepwise Method for Imatinib

Significant Covariates	ΔOFV	*p*-value
Univariate forward inclusion		
RBC on CL/F	−12.50	< 0.001
CRCL on CL/F	−6.56	< 0.05
rs2231142 on CL/F	−9.42	< 0.01
Backward elimination		
RBC on CL/F	7.27	< 0.01
rs2231142 on CL/F	10.35	< 0.01

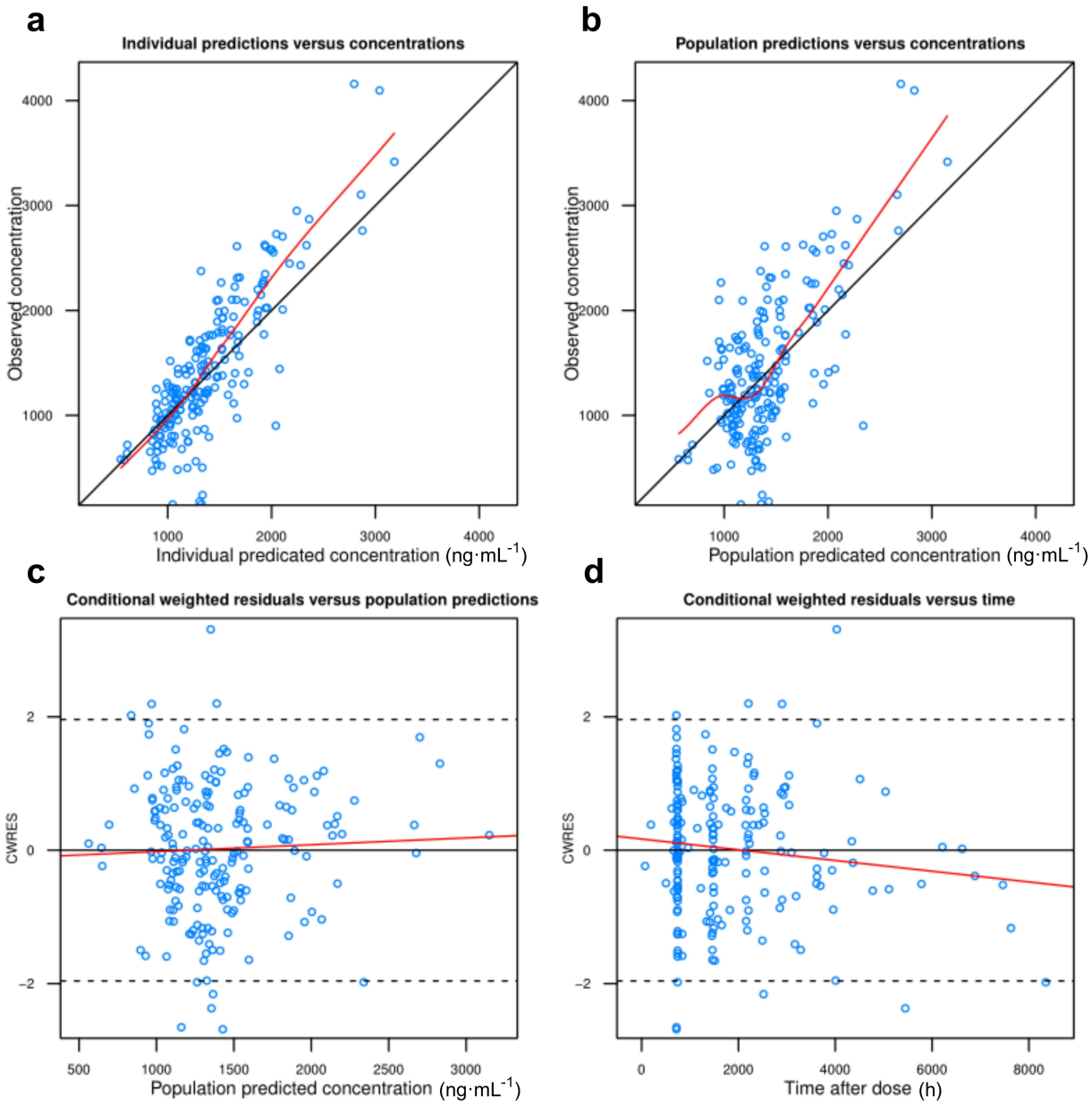

Figure 1 The goodness-of-fit plots of the final model. Observed concentration versus individual predicted concentration (**a**); observed concentration versus population predicted concentration (**b**); CWRES versus population predicted concentration (**c**); CWRES versus time (**d**). The solid black lines are the reference lines, the dotted black lines are the position lines of CWRES at ± 2, and the red lines are the LOESS trend lines.

rate was 99.0%. Additionally, the parameter typical values estimated by the model were equal or similar to the median of the parameter values aggregated from the bootstrap datasets and were all within the 95% CI (2.5–97.5%), indicating that the model is reliable with acceptable stability (Table 3). The pvcVPC shows that the 5th, 50th, and 95th percentiles of observed values fell within the 95% CI of the corresponding simulated data (Figure 2), which shows that the predictability of the final model is acceptable The model was validated using a new dataset consisting of 25 patients, and it showed good predictability again (MPE% = −11.9%, MAPE% = 17.9%). The results obtained were based on population predictions, and it indicated that population predictions ranged from 82.1% to 117.9% of the observations.

Dosing Regimen

The steady-state trough concentrations of imatinib were simulated in different scenarios according to the final model. Under the same circumstances, patients with rs2231142 heterozygous type can achieve higher concentrations. In contrast

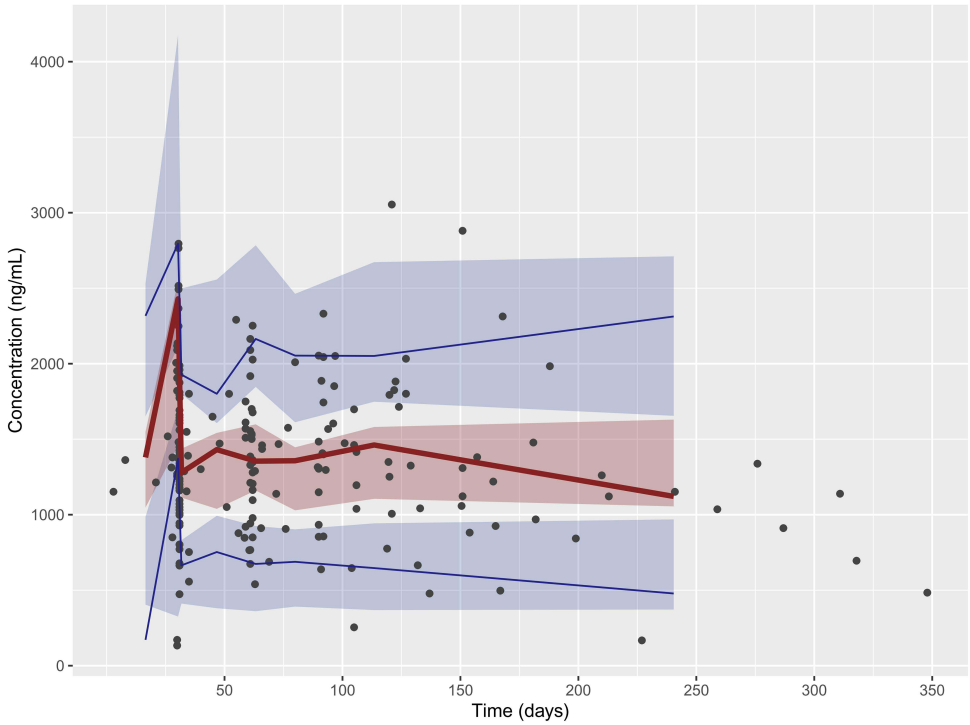

Figure 2 Prediction- and variability-corrected visual predictive check (pvcVPC) plot of the final model. The black dots represent the original observations, the solid lines represent the 5th, 50th, and 95th percentiles of the observations, and the shaded areas represent the 95% confidence intervals of the corresponding quartiles of the data simulated 1000 times.

to the fixed dose regimen of 400 mg each day, a daily dose of 300 mg is enough for patients with rs2231142 GT genotype when RBC is at a lower level (2.9×10^{12}/L), and as RBC rises to 3.9×10^{12}/L and 4.9×10^{12}/L, the recommended dosage is 400 mg and 500 mg daily, respectively. For patients with rs2231142 GG genotype, 500 mg a day is required to achieve the target trough concentration at RBCs of 3.9×10^{12}/L and 4.9×10^{12}/L, while 400 mg a day is a better option when RBC is 2.9×10^{12}/L. The simulation results were plotted in Figure 3.

Discussion

In the present study, a PPK model was developed, for which stability and reliability were demonstrated by multiple validation methods. The typical values estimated by the final model were 9.72 L/h for CL/F and 229 L for V/F, which were close to the results presented in previous studies conducted in patients with GIST (7.97–10.80 L/h for CL/F and 128–284 L for V/F).[7,24,29] However, two PPK models conducted among healthy subjects demonstrated estimated CL/F values much higher than that in this study. This may due to the fact that the majority of the population studied were elderly patients, and about half of them had comorbidities such as hypertension and hyperglycemia. Therefore, the health status of the body likely affects the CL/F of imatinib.[26,30]

Creatinine clearance shows an appreciable correlation with the clearance of many drugs. In this study, clearance of imatinib was not correlated with creatinine clearance, which is consistent with a previous study performed by Delbaldo et al,[24] as imatinib and its metabolites are barely excreted through the kidneys. The correlation coefficient between age and creatinine clearance was −0.67 (Supplementary Figure 2). This negative correlation indicated that creatinine clearance decreased with increasing age; thus, age appeared only in the initially considered covariates and was excluded in the subsequent analysis. A study conducted in CML patients demonstrated a significant effect of WBC on imatinib clearance.[29] The connection between WBC and imatinib clearance was also investigated in this study; however, no such correlation was found in the population described in this study, which is consistent with the results obtained by Delbaldo et al and Shriyan et al, who both excluded WBC in the backward elimination process, although the latter was performed in a CML population.[24,31]

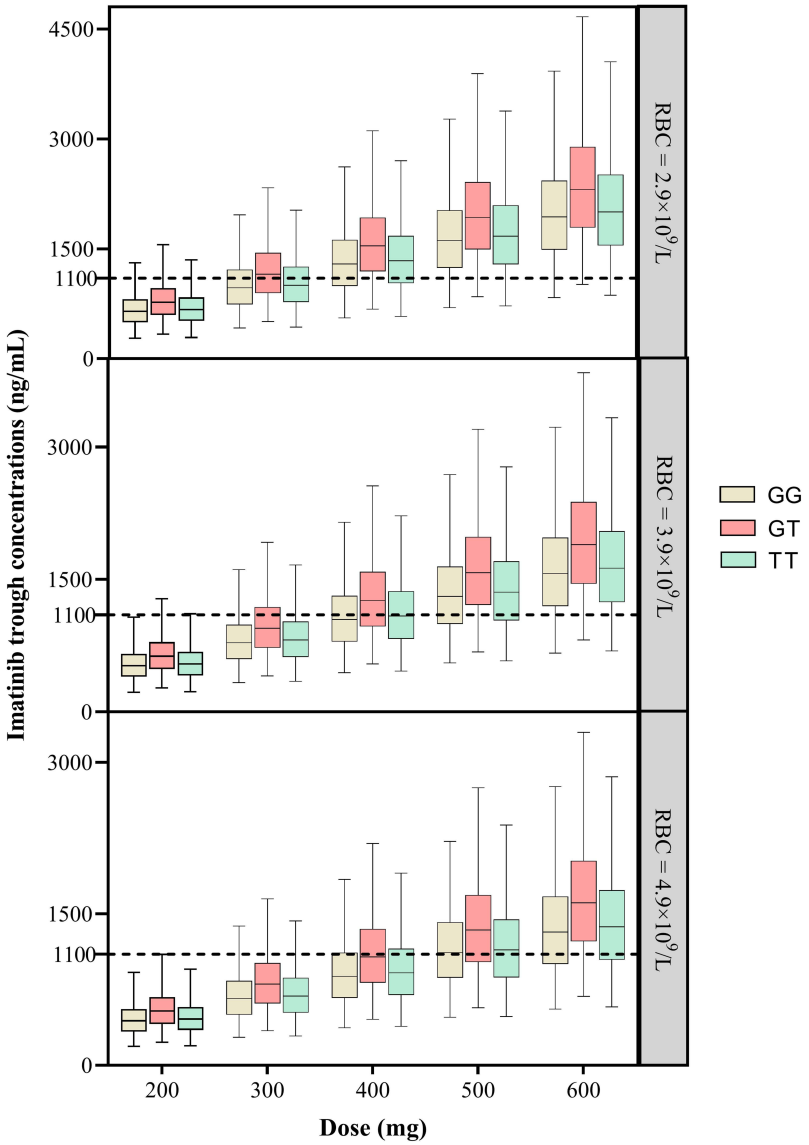

Figure 3 Box plots of simulated steady-state trough concentrations of imatinib (n = 1000) for different dosing regimens (200–600 mg daily) based on different genotypes of rs2231142 (GG, GT and TT) and different RBCs levels (2.9×10^{12}/L, 3.9×10^{12}/L and 4.9×10^{12}/L). The horizontal dashed lines represent the lower limit of the therapeutic concentration threshold (1100 ng/mL).

In covariate modeling, RBC and rs2231142 were identified to be substantially related to the CL/F of imatinib and were incorporated into the model to improve the fit of the model. This is, as far as we know, the first PPK model of imatinib involving genetic polymorphisms for Chinese adults with GIST after surgery. No previous study has reported the effect of RBC on imatinib clearance, which may be attributed to the different populations studied. In the current study, a reduction in RBC by 50% was connected with a 29% drop in imatinib CL/F. This may be due to the correlation that imatinib binds with RBCs, and imatinib can be distributed inside the RBCs.[10] Genetic polymorphisms exert a vital impact on the metabolism and transport of imatinib.[32] To identify this connection, a study was conceived by Petain et al and in their study, *ABCG2* rs2231142 was revealed to significantly impact the clearance of imatinib,[25] especially the heterozygous type, which is consistent with the findings of the present study. Furthermore, rs2231142 has been demonstrated to be a topoisomerase I inhibitor,[33,34] and for primitive hematopoietic stem cells, imatinib was observed to show a rapport with ABCG2.[35] Moreover, rs2231142, a missense coding SNP, may greatly affect the activity of ABCG2 and thus drug transport. The remaining unexplained variability in the final model was 29.6%, suggesting that

other potential elements influencing the pharmacokinetics of imatinib may not be detected, and further studies are needed to identify these underlying factors.

We recommended doses appropriate for patients with different genotypes and different RBC levels to achieve satisfactory concentrations. To our knowledge, this is the first time to do that in postoperative GIST adults. Currently, there is a trend to use individualized dosing to address the wide variation in pharmacokinetics between patients, and then to avoid efficacy being compromised by failure to reach the lower threshold of effective therapeutic concentration.

There are limitations to this study. First, the sample size may not be sufficient to avoid the appearance of potential bias. For example, the statistical differences in the underlying covariates may not be detected since the limited patients enrolled. Second, despite multiple methods were used to validate the model, but almost all patients in the external validation cohort were at the same dose level, which may have an impact on the accuracy of the validation. Third, most patients in this study were recruited from Jiangxi Province, and mutation status of the GISTs were not detected, which may have a negative impact on the extension of the model and dosage recommendations, that is, the recommended doses may be more effective for imatinib-sensitive Chinese patients; thus, a large, multicenter study is required to identify the findings.

Conclusion

In conclusion, a PPK model was establish regarding imatinib in Chinese adults with GIST after surgery, in which RBC and rs2231142 were incorporated as significant covariates in the pharmacokinetics variability of imatinib. These two factors ought to be considered when conducting pharmacokinetic-related studies of imatinib in such a population. Based on the model, dose recommendations were given according to different patient characteristics. Future studies may focus on prospective studies to verify the feasibility of dose recommendations given by this study.

Data Sharing Statement

All datasets or codes generated can be obtained by contacting the corresponding author.

Ethical Approval

Written informed consent was given by all participants and the study was performed following the Declaration of Helsinki and granted by the medical ethics review board of the First Affiliated Hospital of Nanchang University (Medical Ethics No. 12-001, 2021).

Consent for Publication

All named authors agreed to submit the manuscript for publication.

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Disclosure

The authors report no conflicts of interest in this work.

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