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ORIGINAL ARTICLE

**Ian Judson · Peiming Ma · Bin Peng · Jaap Verweij
Amy Racine · Eugenio Donato di Paola
Martine van Glabbeke · Sasa Dimitrijevic
Michelle Scurr · Herlinde Dumez · Allan van Oosterom**

Imatinib pharmacokinetics in patients with gastrointestinal stromal tumour: a retrospective population pharmacokinetic study over time. EORTC Soft Tissue and Bone Sarcoma Group

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Abstract Imatinib pharmacokinetics (PK) may be affected by a number of factors that are related to the disease being treated and to the response of that disease to imatinib. Patients in the phase I and phase II trials conducted by the EORTC in patients with gastrointestinal stromal tumours (GISTs) and other sarcomas had detailed blood sampling for imatinib PK on day 1 and on day 29. Patients with GISTs also had repeat sampling, using a limited sampling strategy, after approximately 12 months on therapy. This population PK study was carried out to examine what covariates affected imatinib PK in GIST patients and what PK changes occurred over time. In the model producing the best fit, low clearance (CL) correlated with low body weight and high granulocyte count, whereas low haemoglobin correlated with low volume of distribution. For a patient with 77% of the median body weight or with 1.87 times the median granulocyte count, the apparent CL is 6.53 l/h, about 70% of the typical apparent CL of 9.33 l/h; for a patient of 84% of the typical haemoglobin level, the volume of distribution is about 70%. Total white blood cell count correlated closely with granulocyte count and there was a moderate correlation between haemoglobin and albumin ($r = 0.454$). There was a trend towards increased imatinib clearance after chronic exposure over 12 months. The typical apparent CL increased 33% from day 1. Nevertheless, the approximate 95% confidence interval of the increase of the typical apparent CL was $33 \pm 34.6\%$, which contains zero. It is not yet clear whether this is a significant factor in the amelioration of imatinib toxicity that occurs with time or is related to disease control, and further work is required to confirm this observation.

Keywords Imatinib · Pharmacokinetics · Gastrointestinal stromal tumours

I. Judson (✉) · M. Scurr
Royal Marsden Hospital,
Fulham Road, London, SW3 6JJ, UK
E-mail: ian.judson@icr.ac.uk
Tel.: +44-20-87224302
Fax: +44-20-86427979

P. Ma · B. Peng · A. Racine
Novartis Pharmaceuticals, East Hanover, NJ, USA

J. Verweij
Department of Medical Oncology,
Erasmus University Medical Center Rotterdam,
Rotterdam, The Netherlands

E. D. di Paola · M. van Glabbeke
EORTC Data Center, Brussels, Belgium

S. Dimitrijevic
Novartis Oncology, Novartis Pharma AG,
Basel, Switzerland

H. Dumez · A. van Oosterom
Department of Oncology, UZ Gasthuisberg,
KU Leuven, Leuven, Belgium

Introduction

Imatinib is a small-molecule tyrosine kinase inhibitor that was first developed for the treatment of chronic myeloid leukaemia (CML), in which disease it acts to inhibit the action of the BCR-ABL fusion protein [6, 7]. In addition to inhibiting ABL, imatinib is also an inhibitor of KIT and PDGFR [4]. Gastrointestinal stromal tumours (GISTs) arise from mesenchymal stem cells that are thought to share common ancestry with the interstitial cells of Cajal that are responsible for coordinating gut peristalsis, as shown by the expression of CD34 and KIT (CD117) shared by Cajal cells and GISTs [13]. In addition, GISTs have a high incidence of activating gain of function mutations in KIT, usually in exon 11 [11]. Such mutations are an early event in the evolution of GISTs and are to be found even in small

tumours of uncertain malignant potential, indicating that activation of KIT is an important oncogenic driving force in this disease. Following the initial report by Joensuu that imatinib could produce tumour regression in GIST [12], early clinical trials began in Europe and the USA in the summer of 2000. A dose-ranging phase I trial in soft tissue sarcomas, mainly in patients with GIST, was conducted in Europe [17], followed by a phase II study at 800 mg in two defined populations of patients with GIST and other sarcomas [18]. A phase II study in GIST comparing doses of 400 mg and 600 mg daily was conducted in the USA [5]. Subsequent phase III trials in GIST comparing 400 mg and 800 mg daily have been completed in Europe and the USA, and have confirmed the safety and activity of imatinib [3, 19].

It has been reported that the side effects associated with imatinib, such as nausea, vomiting, oedema and rash, tend to lessen with time [18]. In addition, there are reports that patients progressing on imatinib may experience disease stabilization when the dose is increased. Pharmacokinetic (PK) studies were performed in the phase I and phase II trials at study entry and on day 29. In addition, additional samples were obtained, using a limited sampling strategy, from patients who had been receiving imatinib for approximately 12 months. These data were analysed to look at PK–pharmacodynamic correlations and to examine the influence of prolonged treatment on the clearance of imatinib.

Methods

Patients in the phase I trial were treated at 400 mg once a day, 300 mg twice a day, 400 mg twice a day and 500 mg twice a day. Following determination that this was a safe dose, patients in the phase II study were treated at 400 mg twice a day. Blood samples were taken for pharmacokinetic analysis on day 1 at the following times: predose, and 1, 2, 3, 4, 8, 12, 14 and 24 h after dosing for patients receiving one daily dose. For patients being dosed twice a day the 12-h sample was taken after the first dose, just prior to the second dose, and the 14-h sample 2 h after the second dose. In both groups of patients, the 24-h sample was prior to the third dose. On day 29 samples were taken predose, and 2, 8 and 24 h afterwards. Those patients still on study at 12 months had samples taken predose and at 2 and 4 h after dosing, and some of these patients were also sampled after 3 months at the same time points.

Samples were centrifuged at 4000 *g* for 15 min, and the plasma was separated and stored at −20°C until analysis. Plasma imatinib concentrations were determined in the Novartis USA bioanalytical laboratory using a liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay [1]. Plasma samples were prepared using a protein precipitation procedure. Sample extracts were analysed using reverse-phase chromatography with a Waters Symmetry column (Waters Corporation, Milford, Mass.) followed by detection with a Sciex API 3000 mass spectrometer (PE Biosystems, Foster City, Calif.). The lower limit of quantification was 4 ng/ml and the assay was fully validated. The accuracy and precision from prestudy validation were $104 \pm 5.64\%$ at the lower limit of quantification and $98.9 \pm 4.56\%$ to $108 \pm 5.09\%$ over the entire concentration range of 4–10,000 ng/ml.

We have previously reported that imatinib PK correlate with certain biochemical parameters (haemoglobin level, white blood cell count (WBC), and albumin level) [13], which may vary during the course of imatinib treatment. When imatinib is administered chronically to GIST patients, certain of these parameters, such as hepatic function, may change significantly. Therefore, a simple data pooling of plasma samples on day 1 (treatment initiation) and from other days (steady-state STI571) may introduce confounding factors biasing the analysis. To avoid such potential bias, the population PK analysis was designed to have two parts, and the final models that led to the data interpretation were called models 1 and 2. The first part included all patients who gave PK samples that were collected on day 1 to assess any covariate effect on imatinib PK. The purpose was to identify sources of PK variability and to determine whether any of the disease-related factors and demographic variables might influence the PK of imatinib at the time of initial administration of imatinib. The covariates included were patient demographics (body weight, age, and gender) and other pretreatment variables listed in Table 1. Although considered potentially important, α_1-acid glycoprotein levels were not measured at the time of this analysis.

Information on concomitant medications was collected at the time of treatment initiation and at disease

Table 1 Pretreatment variables considered for STI571 PK association

Dichotomous variables	Continuous variables
Primary tumour or recurrence present	Time since initial diagnosis of sarcoma in days
Liver metastases present	White blood cells as multiples of 10^9 per litre
Stomach lesions	Granulocytes as multiples of 10^9 per litre
GIST histology	Platelets as multiples of 10^9 per litre
GI origin of the disease	Haemoglobin in micromoles per litre
Abdominal origin of the disease	Creatinine in micromoles per litre
Prior surgery	Creatinine clearance, derived from serum creatinine concentration by the Cockcroft-Gault formula
Prior radiotherapy	Bilirubin in micromoles per litre
Prior chemotherapy	Alkaline phosphatase, expressed as the fraction of the upper normal limit
	Aspartate aminotransferase, expressed as the fraction of the upper normal limit
	Alanine aminotransferase, expressed as the fraction of the upper normal limit
	Albumin in grams per litre

assessment times but was unreliable at the time of late PK sample collection. Hence we did not attempt to relate PK data to administration of potential cytochrome P450-interactive drugs. The use of such agents was severely restricted in this study and major interactions were not expected. The second part of the analysis included all patients who had any imatinib PK samples collected on day 1 and day 29, and in the extension phase. The purpose was to determine whether changes occur in imatinib PK and exposure over time. For the reason mentioned above, only demographic variables were considered as possibly affecting the imatinib PK in this part of the analysis, and only steady-state PK samples on day 29 and in the extension phase were included. The term "steady state" means that the same dosage was maintained for ≥7 days.

A population approach with nonlinear mixed effects modelling was used for the pharmacokinetic analysis. The time course of plasma concentrations of STI571 was assumed to follow a one-compartment model with zero-order absorption and first-order elimination processes (Fig. 1) [15].

In the diagram, D_1 is a duration constant of the zero-order input for the absorption process of imatinib from the GI tract to the systemic circulation, or the central compartment, and low clearance (CL) the elimination clearance of imatinib.

An ordinary differential equation (ODE) was used to characterize the model, and the solution to the ODE represents the amount of imatinib, which, divided by the volume V of the central compartment, gives the plasma concentration value as a function of time.

The three parameters CL, D_1 and V described above represent the fixed effects in the model. A key assumption in this PK modelling analysis is the applicability of the principle of superposition in relation to the multiple dose regimen, which is reasonable since the mean AUC and C_{max} of imatinib in CML patients have been shown to be dose proportional in the dose range of 25–1000 mg [1].

The mean absolute bioavailability of imatinib, which is a highly soluble and highly permeable drug, is close to one [16] and the parameters CL and V described above are in fact the apparent clearance (CL/f) and the apparent volume of distribution (V/f), respectively.

Multiplicative random effects were studied on PK parameters of CL and V. If θ represents either of CL and V, then a quantity of the form $\beta \exp(\eta)$, instead of β alone, was in the functional form of the concentration,

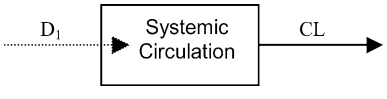

Fig. 1 One-compartment model with zero-order absorption and first-order elimination. D_1 is a duration constant of the zero-order input for the absorption process of imatinib from the GI tract to the systemic circulation, or the central compartment, and CL the elimination clearance of imatinib

where η is a random effect and assumed to be normally distributed with mean zero. In doing so, the value of the parameter β can be viewed as being representative of the patient population and is, therefore, called a typical value.

In general, the random effects were allowed to have arbitrary correlation, i.e., a full covariance matrix was assumed, except when numerical difficulty in the computational algorithm compelled a simplification or, for example, the full covariance structure did not significantly improve a model over the simpler diagonal variance structure. Also assigned to the model were independent random errors, representing intrapatient variability, model misspecification, error in the analytical measurement (e.g. due to assay quantification limit), and residual random noise.

In testing if a baseline covariate x has any influence on the PK parameters CL and V in the initial phase of imatinib administration, the following functional form was used as a multiplier to the CL-covariate and V-covariate model, in order to establish a pair of models of hierarchy (i.e. one is a submodel of the other when the parameter is constrained to zero for a continuous variable, or one for a categorical variable):

- $(x/x_m)^\theta$ for a continuous variable x with a median value of x_m
- θ^x for a dichotomous variable taking the value of one (for yes) and zero (for no)

where θ is a parameter to be estimated. The final models were developed from progressively more elaborate models, considered to be representative of imatinib PK. The selection of the final model was based on usual diagnostic techniques such as examination of the residual plot and correlation plots of predicted versus observed concentrations and, when the models were related hierarchically, the difference of the minimum objective function (MOF) values was taken as a guide for favouring a more complex one. For example, a reduction of MOF of more than 6.63 is considered to be significant at the 0.01 level, approximated by χ^2 with one degree of freedom. Other factors, such as the size of the estimated random effects, random errors, and standard errors of parameter estimates were also taken into account for retaining models, especially in the case that convergence is not unique.

The models were developed with the NONMEM (non-linear mixed effect modelling) software, version V [2]. A first-order conditional method with interaction was used in the whole model-building process.

Results

A total of 43 soft tissue sarcoma (STS) and GIST patients (27 male and 16 female) were included in the analysis. These patients provided a total of 517 plasma samples in the study: 319 samples from 42 patients on day 1; 124 samples from 33 patients on day 29; and 74

samples from 24 patients in the extension phase. As previously reported, there was a large degree of inter-patient variability.

For the first part of the PK analysis, the final model showed that the haemoglobin level, weight, and granulocyte count were significantly related to CL and V of imatinib in the initial phase of the administration. In the model providing the best fit (model 1), the parameter structure of CL and V was identified as:

$$\mathrm{CL} = \theta_{\mathrm{CL}} \times (\text{body weight}/66.75)^{\beta_2} \times (\text{granulocyte}/4.7)^{\beta_3}\, exp(\eta_{\mathrm{CL}})$$

and

$$V = \theta_{\mathrm{V}} \times (\text{haemoglobin}/7.95)^{\beta_1}\, \exp(\eta_{\mathrm{V}})$$

where the θs represent typical values of the PK parameters, β_1, β_2, and β_3 are fixed effects quantifying the influence of haemoglobin level, body weight, and granulocyte count on CL and V, and η's random effects. PK parameter estimates from NONMEM output for model 1 are shown in Table 2.

The model predicted that, for a 66.75-kg patient with a baseline granulocyte count of 4.7×10^9/l and haemoglobin level of 7.95 μmol/l, the apparent CL and V at the initial phase of imatinib administration would be, respectively, 9.33 l/h and 184 l.

From the model, high CL was correlated with high body weight and low granulocyte count. Therefore, low granulocyte count was correlated with low AUC. The volume of distribution V was correlated with high haemoglobin.

In Table 3 these data are also presented stratified into three prognostic groups centred around the mean, i.e. lowest 25%, mean ±25%, highest 25%, to demonstrate the range of values. No PK parameters showed a correlation in GIST patients with response, time to response or time to progression, but the numbers of evaluated patients were small and this is not definitive. Some of the patients had a low albumin (25% <36 g/l, 10% <31 g/l, 5% <25 g/l) at the time of study entry, which improved with response to treatment in the majority. Similarly the side effects decreased in severity over time, as previously reported [18].

Table 2 Imatinib PK parameter estimates from model 1 on day 1: fixed effects and variances of random effects (and standard errors)

θ_{CL} (l/h)	θ_{V} (l)	Var(η_{CL})	Var(η_{V})	Cov(η_{CL},η_{V})	D_1 (h)	β_1	β_2	β_3
9.33 (0.98)	184 (14)	0.301 (0.11)	0.176 (0.04)	0.093 (0.06)	1.64 (0.19)	2.03 (0.47)	1.34 (0.35)	−0.57 (0.26)

Table 3 Distribution of PK parameters within prognostic groups. The following table gives the mean and coefficient of variation (CV) of PK parameters in the different prognostic subgroups. Continuous prognostic factors have been categorized in three groups, where extreme categories include at least 25% of the cases. It shows that the standardized AUC may vary by a factor of 2 between extreme categories

Prognostic group	Category	*n*	CL		V		$t_{1/2}$		Dose-standardized AUC	
			Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
All		42	11.95	73	197	52	14.06	52	124	64
Weight (kg)	<57.1	11	6.07	42	169	39	20.68	41	198	49
	57.1–77.8	20	13.23	67	200	60	12.19	45	106	57
	>77.8	11	15.51	64	217	46	10.83	44	82	41
Granulocyte (10^9/l)	<3.5	12	18.11	60	257	39	12.52	56	77	59
	3.5–5.8	17	9.58	46	162	68	12.28	42	140	68
	>5.8	13	9.36	91	186	37	17.81	49	147	45
Haemoglobin (mmol/l)	<7	11	9.95	95	123	58	10.94	50	162	67
	7–8.8	20	10.67	72	185	34	15.44	49	129	51
	>8.8	10	17.33	50	294	44	12.91	45	67	34
Platelets (10^9/l)	<251	13	14.22	69	245	45	14.8	49	100	58
	251–400	18	11.69	64	190	52	13.76	53	125	75
	>400	11	9.68	96	150	52	13.68	58	151	48
Albumin (g/l)	<36.1	12	7.21	53	128	44	14.76	57	181	56
	36.1–42	18	13.59	75	209	50	13.71	57	111	60
	>42	12	14.23	59	246	43	13.88	41	86	36
Creatinine (μmol/l)	<80	12	8.18	54	153	43	15.52	52	160	50
	80–100	16	12.74	71	191	37	13.25	52	116	78
	>100	14	14.28	73	240	59	13.73	54	103	55
Gender	Male	27	14.52	67	220	53	12.66	52	100	61
	Female	15	7.32	40	154	33	16.59	48	167	55
Prior surgery	Yes	34	12.66	73	213	47	14.82	51	115	57
	No	8	8.92	55	128	70	10.85	49	161	75
GIST histology	Yes	35	12.75	71	203	53	13.45	52	112	55
	No	7	7.95	61	163	43	17.11	50	183	70

For the second part of the PK analysis, the parameter structure of CL and V were identified as:

$$\mathrm{CL} = \theta_{\mathrm{CL}} \times (\text{body weight}/67.5)^{\beta} \exp(\eta_{\mathrm{CL}})$$

where θ_{CL} takes different values, respectively, on day 1 and day 29, and in the extension phase, and $V = \theta_{\mathrm{V}} \exp(\eta_{\mathrm{V}})$. Weight became insignificant when all imatinib PK data were included, but was kept in the final model (model 2). Table 4 shows parameter estimates from the NONMEM output.

Summary statistics of derived individual PK parameters on day 1 and day 29, and the extension phase from model 2 are displayed in Table 5. The coefficient of variation for CL was about 50%. The mean individual apparent clearances derived from model 2 were computed to be 9.23, 8.71 and 14.74 l/h, respectively, on day 1 and day 29, and in the extension phase. These values are different from those shown in Table 4. The values in Table 4 are model-estimated typical CL on day 1 and day 29, and in the extension phase for a typical patient with median age and median granulocyte count. These values were determined in the process by which the final model was generated. Also determined in the modelling process were individual differences from the typical profile, which were determined by the estimated fixed-effect parameters. These differences were caused by factors that include body weight, granulocyte count, and other random effects, and resulted in differences in the values of individual parameters such as CL. The means of these individual CLs of all periods were computed as a second set of values described above. Each of the mean CL values was greater than the estimated typical CL value, close to the median, showing that CL has a skewed distribution. Both Tables 4 and 5 suggest that CL changes over time. The difference in MOF values between model 2 and the model with constant CL over time was 33.7, with a P value with two degrees of freedom from the approximate χ^2-test of less than 0.001. The typical apparent clearance showed a modest increase of 33% in the extension phase compared to that on day 1. Nevertheless, the approximate 95% confidence interval of the increase in the typical apparent clearances was $33 \pm 34.6\%$, which contains zero. Here the quantity 34.6% was computed from 1.96×(standard error for the difference in the typical apparent clearance in the extension phase and that on day 1)/(typical apparent clearance on day 1).

The increase in the apparent clearance, if true, should lead to decreasing exposure. The mean dose-normalized daily AUC values [i.e. (daily dose in μg)/(CL in l/h)] derived from model 2 on day 1 and day 29, and in the extension phase were 139,156, and 80 ng h/ml/mg (Table 5 and Fig. 2). Here AUC on day 1 should be understood as having been calculated from 0 to ∞ with administration of the first dose (or only dose if once-daily dosing) at time zero, plus AUC contributed to by the second dose if twice-daily dosing, but no additional doses. The decrease in AUC in the extension phase over that on day 1 was 42%.

Error variability was quite large. The multiplicative error SDs for the two models were 36% and 34%, respectively; the additive error SDs were 139 ng/ml and 273 ng/ml, respectively.

Diagnostic plots for models 1 and 2 are provided in Figs. 3 and 4, respectively. Figures 3a,b and 4a,b display plots of population-predicted and individual-predicted values versus observed values, where a point on the diagonal line signifies that the predicted value is equal to the observed value. Besides the large variability that was not adequately explained, the models give overall fair fits. Figures 3c and 4c show the population predicted concentrations from the model fitting versus residual values, defined as the difference between observed and population predicted values. Figures 3d and 4d present the population predicted concentration versus absolute values of the weighted residuals, formed by transforming the residuals so that under the model, assuming the true values of the population parameters are given by the estimates of those parameters, all weighted residuals have unit variance and are uncorrelated. The points are scattered with no particular pattern, and the nearly even locally weighted-regression line essentially supports the

Table 5 Summary statistics of derived individual PK parameter values on days 1, 29 and extended phase from model 2

Parameter	Mean	SD	Minimum	Median	Maximum
Day 1 ($n = 42$)					
CL (l/h)	9.23	4.61	2.37	8.83	22.88
V (l)	212	118	54	179	530
$t_{1/2}$ (h)	16.41	5.53	7.55	16.41	31.91
AUC (ng h/ml/mg)	139	80	44	113	423
Day 29 ($n = 33$)					
CL (l/h)	8.71	4.78	2.22	8.28	21.48
V (l)	219	129	60	187	530
$t_{1/2}$ (h)	18.24	6.49	8.04	18.46	33.99
AUC (ng h/ml/mg)	156	97	47	121	450
Extension phase ($n = 24$)					
CL (l/h)	14.74	6.37	5.10	13.51	30.42
V (l)	248	133	79	217	530
$t_{1/2}$ (h)	11.73	4.05	5.68	10.82	20.19
AUC (ng h/ml/mg)	80	36	33	74	196

Table 4 Imatinib PK parameter estimates over the study duration: fixed effects and variances of random effects (and their standard errors)

θ_{CL} (l/h)			θ_{V} (l)	$\mathrm{Var}(\eta_{\mathrm{CL}})$	$\mathrm{Var}(\eta_{\mathrm{V}})$	$\mathrm{Cov}(\eta_{\mathrm{CL}},\eta_{\mathrm{V}})$	D_1 (h)	β
Day 1	Day 29	Extension phase						
7.96 (1.01)	7.48 (0.71)	10.6 (1.16)	182 (16)	0.305 (0.073)	0.34 (0.073)	0.237 (0.061)	1.51 (0.19)	0.002 (0.14)

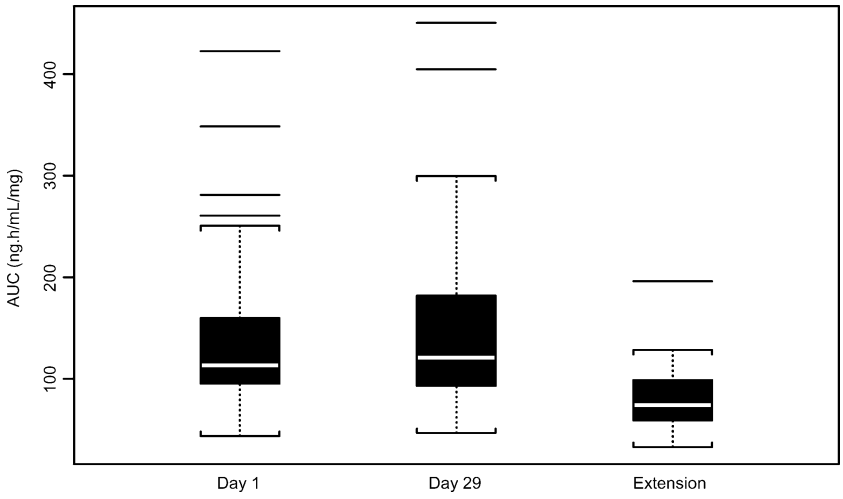

Fig. 2 Dose-normalized AUC distributions on day 1 and day 29, and in the extension phase

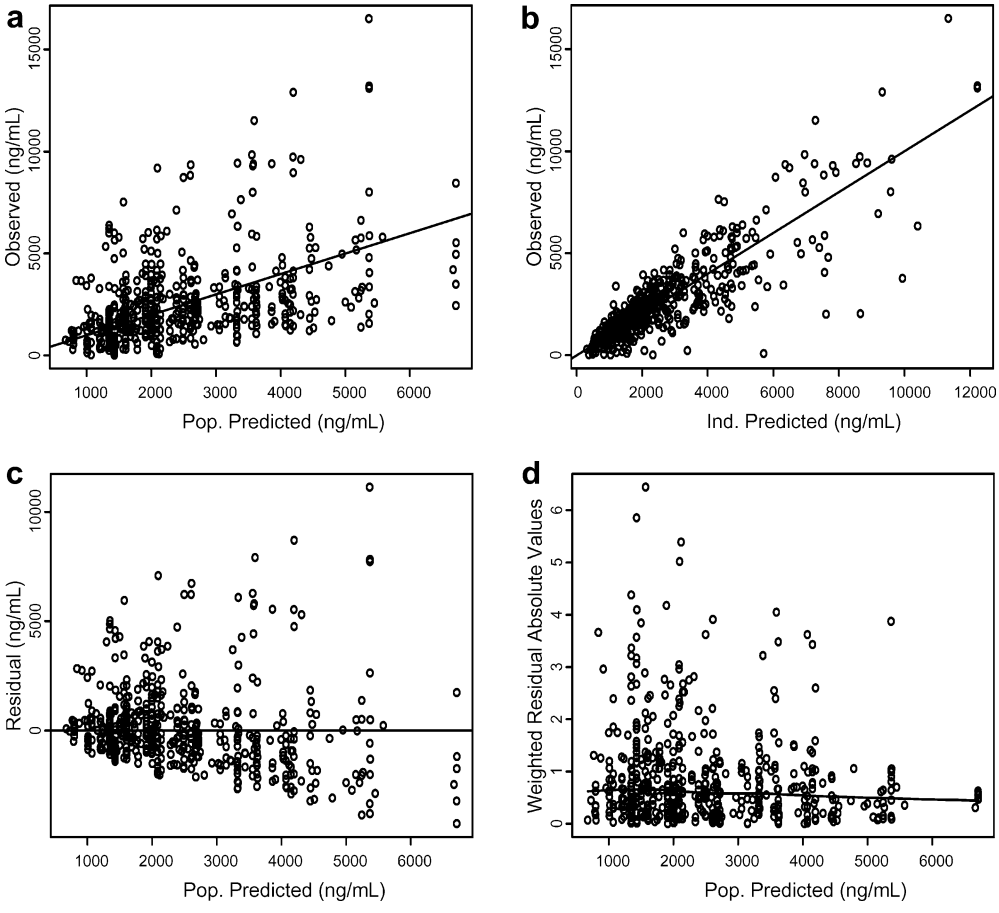

Fig. 3 Diagnostic plots for population PK model on day 1 (model 1): **a** population predicted versus observed values; **b** individual predicted versus observed values; **c** population predicted concentrations from model fitting versus residual values, i.e. the difference between observed and population predicted values; **d** population predicted concentration versus absolute values of the weighted residuals, formed by transforming the residuals so that under the model, assuming the true values of the population parameters are given by the estimates of those parameters, all weighted residuals have unit variance and are uncorrelated

constancy of multiplicative errors, showing a reasonable model fit to the data.

A modest correlation between albumin and haemoglobin levels at baseline was found with a correlation coefficient of 0.454. A stronger correlation existed between granulocyte count and WBC with a correlation coefficient of 0.93 after excluding an outlying value (patient ID 35 of centre 613: WBC 25×10^9/l and granulocytes 3.3×10^9/l).

Discussion

In the phase I study the principal side effects observed during the first 8 weeks of therapy were skin rash in 22 patients (56%) (in only 2 patients was this severe requiring dose modification), oedema in 30 (75%), periorbital oedema in 12 (25%), diarrhoea in 14 (35%), nausea in 17 (43%), vomiting in 11 (27%), conjunctivi-

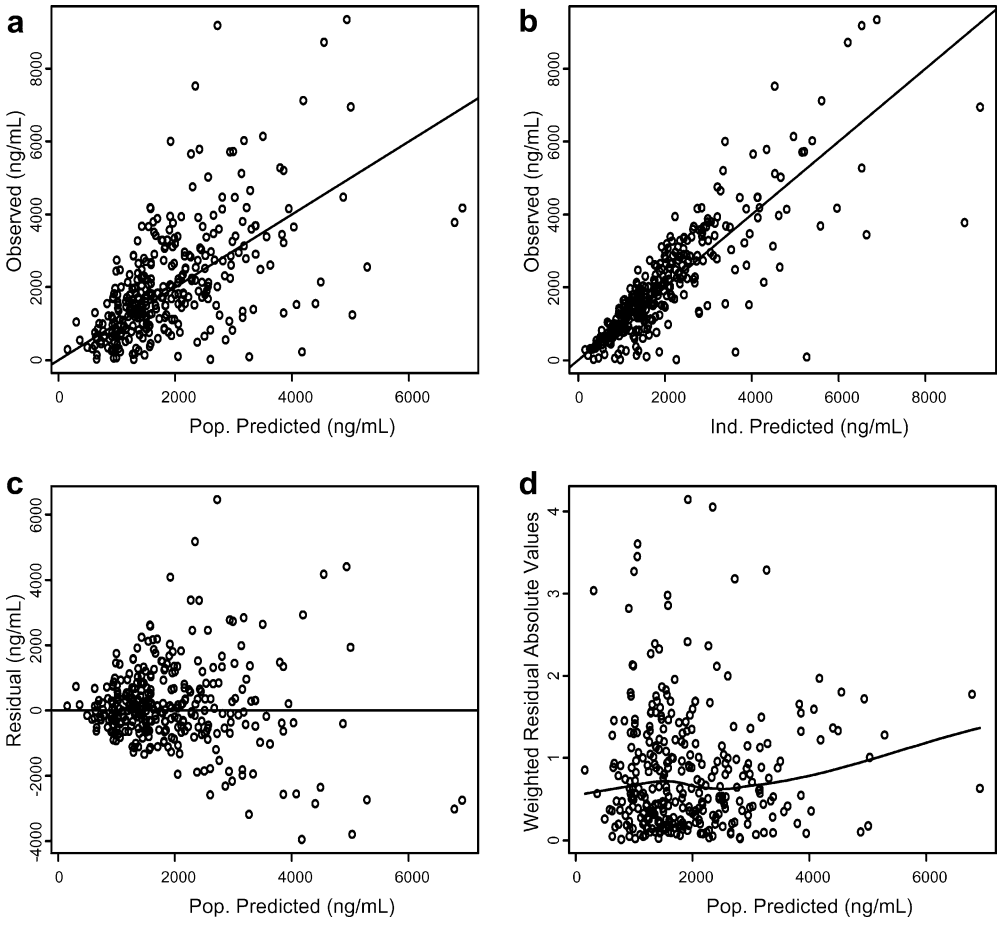

Fig. 4 Diagnostic plots for population PK model based on all imatinib data (model 2): **a** population predicted versus observed values; **b** individual predicted versus observed values; **c** population predicted concentrations from model fitting versus residual values, i.e. the difference between observed and population predicted values; **d** population predicted concentration versus absolute values of the weighted residuals, formed by transforming the residuals so that under the model, assuming the true values of the population parameters are given by the estimates of those parameters, all weighted residuals have unit variance and are uncorrelated

tis, bleeding sclerae, and change of taste. In three patients intratumoral bleeding (one with perforation to the abdomen) was observed. Mild anaemia and neutropenia grade 2 or 3 were reported, and this contributed to the decision to reduce the dose in a number of patients. In the phase II trial the most frequent side effects reported were anaemia (92%), oedema (particularly periorbital oedema) (84%), skin rash (69%), fatigue (76%), nausea (57%) and granulocytopenia (47%). Most of these side effects were mild to moderate and tended to occur in the first 8 weeks of treatment. Amelioration of side effects with time has been reported [18].

The correlation between PK and baseline patient characteristics suggests a strong association between the day-1 AUC and haematological and biological parameters (haemoglobin and granulocytes). A previous study in a population of patients with unresectable or metastatic malignant GIST [13] has shown that the apparent clearance increases with albumin levels and decreases when WBC increases, and that the apparent volume of distribution increases with albumin levels. However, it was found in the present analysis that the volume of distribution was most closely correlated with haemoglobin, perhaps due to drug binding. A modest correlation between haemoglobin and albumin was demonstrated. In this analysis, granulocyte count, more than WBC, was found to be important in the covariate model of CL. However, this is consistent with our previous results since the WBC correlated closely with the granulocyte count.

We do not have data on α1 acid glycoprotein (AGP) levels at the times of PK sampling. Data from CML patients suggests that the raised AGP levels often seen in cancer patients can result in increased plasma imatinib levels, but at least in the context of CML this may be associated with lower drug levels in leukaemic blasts, presumably because of a reduced free drug fraction [8]. Given that AGP levels may correlate with disease activity and disease burden it would be reasonable to assume that AGP levels fall over time in patients with GIST who are responding to imatinib. This would have the effect of lowering plasma imatinib levels, hence increasing clearance, but might not affect drug delivery to tumour.

So in conclusion, there is some evidence that the apparent clearance of imatinib may increase over time in patients with advanced STS, including GIST. After long-term treatment, mean imatinib clearance increased by 33% compared to clearance on day 1. This finding is not conclusive since the 95% confidence limits were −1.6% and 67.6%. The increase in the apparent clearance leads to a decreased exposure. It is possible that such a decrease could go some way towards explaining the reduction in imatinib-related side effects that occurs

with time. Given the large interpatient variability in clearance and AUC, it is currently not possible to determine whether or not pharmacokinetic factors might play a role in the development of resistance to imatinib. Mutations affecting the KIT binding site and activation of alternative proliferative pathways offer more likely explanations. However, stabilization of progressive disease following an increase in imatinib dosage has been described [20]. A recent report by Heinrich et al. showing that in GIST tumours with wild-type *KIT*, mutations in *PDGFR-A* may be responsible for constitutive activation of signalling pathways may also provide some insights into the development of resistance in this disease [9]. Increasingly, knowledge of mutation type can be used to predict the response of GIST to imatinib [10]. Further work is required to determine whether or not a late increase in imatinib clearance truly does occur in GIST patients and the extent to which this contributes to alterations in response and disease control.

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