


# Imatinib Pharmacokinetics in a Large Observational Cohort of Gastrointestinal Stromal Tumour Patients

Sheima Farag<sup>1</sup>  · Remy B. Verheijen<sup>2</sup> · J. Martijn Kerst<sup>1</sup> · Annemiek Cats<sup>3</sup> · Alwin D. R. Huitema<sup>2</sup> · Neeltje Steeghs<sup>1</sup>

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## Abstract

**Background** Low trough imatinib concentration ( $C_{\min}$ ) values have been associated with poor clinical outcomes in gastrointestinal stromal tumour (GIST) patients. This study describes the pharmacokinetics of imatinib in a large cohort of GIST patients in routine clinical care.

**Methods** An observational study was performed in imatinib-treated GIST patients. Patient and tumour characteristics were derived from the Dutch GIST Registry and medical records. Imatinib concentrations were measured by liquid chromatography with tandem mass spectrometry. The analyses included the occurrence of a low imatinib  $C_{\min}$  ( $<1000 \mu\text{g/L}$ ), the change in the  $C_{\min}$  over time and the correlation between exposure and response.

**Results** In total, 421 plasma samples were available from 108 GIST patients. Most patients (79.6 %) received an imatinib dose of 400 mg. The inter- and inpatient variabilities in  $C_{\min}$  were 54 and 23 %, respectively. In the first steady-state sample, 44.4 % of patients presented with  $C_{\min}$  values  $<1000 \mu\text{g/L}$ ; 32.4 % of patients had values  $<1000 \mu\text{g/L}$  in  $>75$  % of their samples. Only 33.3 % of patients had  $C_{\min}$  values  $\geq 1000 \mu\text{g/L}$  in all measured

samples. No decrease in  $C_{\min}$  over time was found ( $P > 0.05$ ). Fifty-seven (91.9 %) of 62 palliative-treated patients had a tumour response (median  $C_{\min}$  1271  $\mu\text{g/L}$ ). Five palliative patients (8.1 %) did not respond (median  $C_{\min}$  920  $\mu\text{g/L}$ ). Given the limited number of non-responders in this cohort, no statistically significant association with clinical benefit could be demonstrated.

**Conclusion** In routine clinical care, one third of GIST patients are systematically underexposed with a fixed dose of imatinib. Prospective clinical studies are needed to investigate the value of  $C_{\min}$ -guided imatinib dosing in GIST patients.

## Key Points

A retrospective observational cohort study was conducted to assess underexposure in imatinib-treated gastrointestinal stromal tumour (GIST) patients in routine clinical care.

In routine clinical care, 32.4 % of imatinib-treated GIST patients were systematically underexposed, with trough plasma concentration ( $C_{\min}$ ) values  $<1000 \mu\text{g/L}$ .

Further prospective clinical studies are needed to investigate the value of  $C_{\min}$ -guided imatinib dosing in GIST patients.

✉ Sheima Farag  
s.farag@nki.nl

<sup>1</sup> Department of Medical Oncology and Clinical Pharmacology, Netherlands Cancer Institute–Antoni van Leeuwenhoek, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

<sup>2</sup> Department of Pharmacy and Pharmacology, Netherlands Cancer Institute–Antoni van Leeuwenhoek, Louwesweg 6, 1066 EC Amsterdam, The Netherlands

<sup>3</sup> Department of Gastroenterology, Netherlands Cancer Institute–Antoni van Leeuwenhoek, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

## 1 Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal malignancies arising from the gastrointestinal tract. Activating mutations in KIT proto-

oncogene receptor tyrosine kinase (*KIT*) or platelet-derived growth factor receptor (*PDGFR*), resulting in activation of the tyrosine kinase signalling pathway, are considered to be the main molecular drivers in GIST. Imatinib is a tyrosine kinase inhibitor (TKI), which targets protein kinases such as Bcr-Abl, *KIT* and *PDGFR*-A and -B [1]. Since the introduction of imatinib, survival has improved spectacularly in advanced GIST patients, and recurrence-free survival has improved in the adjuvant setting. The recommended dose of imatinib is 400 mg, based on previous phase III studies [2, 3]. However, a large variability in plasma imatinib concentrations is observed during treatment [4, 5]. This variability may be caused by a range of factors. Imatinib is metabolized by cytochrome P450 (CYP) 3A4 and CYP3A5, and is also a substrate for drug transporters such as P-glycoprotein (P-gp; ATP-binding cassette sub-family B member 1 [ABCB1]) and breast cancer resistance protein (BCRP; ATP-binding cassette sub-family G member 2 [ABCG2]). Exposure may therefore be influenced by genetic polymorphisms and co-administered drugs [6, 7]. In addition, patients undergoing a major gastrectomy have been shown to have significantly lower  $C_{\min}$  values than other patients [8], and one study has reported a significant decrease in exposure to imatinib over time [9].

Several trials have found a correlation between higher plasma imatinib concentrations and better response to treatment in GIST [4, 10–12] and chronic myeloid leukaemia (CML) [13–15]. Given the increasing evidence that exposure is relevant to clinical outcomes and the large variability in pharmacokinetics, which may be even larger in routine clinical care than in clinical trials, measurement of plasma imatinib concentrations may be useful to guide treatment with this drug. Over the last 3 years, plasma samples have been drawn from GIST patients during routine outpatient visits at our institute. This study describes the pharmacokinetics and occurrence of underexposure to imatinib in a large observational cohort of GIST patients, with over 400 concentrations measured in more than 100 patients during routine outpatient care.

## 2 Methods

### 2.1 Patients

All GIST patients treated with imatinib at the outpatient clinic of the Netherlands Cancer Institute (NKI) were identified retrospectively and included in this study. Identification was done through a search in the database of the Dutch GIST Registry, containing all patients diagnosed with GIST from 2009 to 2014 and treated at five GIST centres in the Netherlands. Only patients treated at the NKI

were included. Patients who were diagnosed before 2009 and had one or more plasma imatinib concentrations measured were identified separately, and their data were added manually.

### 2.2 Variables

Patient characteristics (sex and ethnicity) and tumour characteristics (location, size, mitotic index and mutation status) were extracted from the Dutch GIST Registry. The mutation analysis protocol included analysis of *KIT* (exons 9, 11, 13 and 17) and *PDGFRA* (exons 12, 14 and 18) by Sanger sequencing. Sequencing was performed on a capillary sequencer (ABI 3730 DNA Analyzer; Life Technologies, USA), and mutation analysis was performed using specific software (MutationSurveyer; Softgenetics, USA).

Also, the treatment objective [palliative or (neo-)adjuvant], imatinib dose, dosing schedule and adverse events were included in the analysis. Past surgeries for GIST and surgery results were entered, as were concomitant medication and medical history. For patients diagnosed before 2009, patient files were used for extracting the aforementioned variables. Response evaluations were derived from regularly performed computed tomography (CT) scans and were performed according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. The best overall response was defined as the best response recorded from the start of imatinib treatment until disease progression/recurrence. Patients were classified as responders if their best response was found to be a complete response or a partial response. Patients were classified as non-responders if stable disease or progressive disease was their best response.

### 2.3 Pharmacokinetics

Blood samples were drawn during regularly scheduled visits at the outpatient clinic. The time of the last intake of imatinib and the time of the blood sampling were recorded. Plasma imatinib concentrations were determined using a validated liquid chromatography assay with tandem mass spectrometry [16]. An estimate of the imatinib  $C_{\min}$  was calculated on the basis of the measured concentration and the interval between the last ingested dose and the sampling time, using the algorithm developed by Wang et al. [17]. Adequate plasma imatinib concentrations were defined as imatinib  $\geq 1000$   $\mu\text{g/L}$ , as described in previous studies [13, 15, 18]. For the analysis, the first steady-state imatinib  $C_{\min}$  was used. A representative  $C_{\min}$  was defined as the first representative sample at least 2 weeks after the start of imatinib treatment.

## 2.4 Statistical Analysis

Statistical analyses were executed using IBM SPSS Statistics 20 and R version 3.2.2 software [19]. Univariate and multivariate Cox regression, using relevant characteristics such as the *KIT* mutational status and the imatinib dose, were used for assessing the correlations of exposure to imatinib and time on imatinib treatment with the time to progression (TTP). Also, exploratory analyses using non-linear mixed-effects modelling were conducted to evaluate changes in the imatinib  $C_{\min}$  over time. Inter- and inpatient variabilities were calculated using coefficients of variation. The association between imatinib  $C_{\min}$  values and clinical and demographic variables—such as age, sex, tumour site, surgery and tumour characteristics—was assessed using independent Mann–Whitney *U* tests. All tests were two sided, and a *P* value of <0.05 was considered significant.

## 3 Results

Between January 2009 and May 2014, 111 patients who received imatinib therapy were identified from the Dutch GIST Registry database. Not all patients had known imatinib  $C_{\min}$  values. From August 2012 to December 2014, 582 plasma imatinib concentrations were measured in 123 GIST patients. An additional 33 patients who started imatinib treatment before 2009 and had imatinib drug concentrations measured were identified at the outpatient clinic. All samples below the lower limit of quantification were excluded, in case this was due to a planned end of treatment or interruption due to adverse events. Also, samples with a missing time of the last dose or of sampling and samples drawn within 2 weeks after the start of imatinib treatment were excluded. This resulted in 421 representative plasma imatinib concentrations from 108 patients included in the analysis. The median sample frequency per patient was 3 (range 1–11).

Patient and tumour characteristics are described in Table 1. More than half of the cohort consisted of men ( $n = 60$ , 56.5 %), and the median age was 60 years (range 28–87) (Table 1).

An overview of the distribution of the calculated imatinib  $C_{\min}$  values in the patients studied in this cohort is given in Table 2. The median steady-state  $C_{\min}$  was 1082  $\mu\text{g/L}$ . Sixty patients (55.6 %) had adequate  $C_{\min}$  values at steady state (Fig. 1). Overall, 32.4 % of patients showed low imatinib  $C_{\min}$  values in >75 % of their samples, and 33.3 % of patients showed adequate imatinib  $C_{\min}$  values in all measured samples. Exposure to imatinib showed larger inter- and inpatient variabilities, with relative standard deviations of 54 and 23 %, respectively.

**Table 1** Characteristics of the patients

Characteristic	Patients, $n = 108$
Sex: male [ $n$ (%)]	60 (55.6)
Age [years; median (range)]	60 (28–87)
Tumour status [ $n$ (%)]	
Localized	59 (54.6)
Metastasized	49 (45.4)
Treatment objective [ $n$ (%)]	
Neo-adjuvant	16 (14.8)
Adjuvant	30 (27.8)
Palliative	62 (57.4)
Location of primary tumour [ $n$ (%)]	
Stomach	46 (42.6)
Small bowel	44 (40.7)
Duodenum	2 (1.9)
Rectum	7 (6.5)
Oesophagus	2 (1.9)
Colon	1 (0.9)
Unknown	6 (5.5)
Primary tumour size [mm; median (range)]	100 (19–300)
Mutation status [ $n$ (%)]	
<i>KIT</i> exon 11	76 (70.4)
<i>KIT</i> exon 9	9 (8.3)
<i>KIT</i> exon 13	1 (0.9)
<i>KIT</i> exon 17	3 (2.8)
<i>PDGFR</i> exon 14	1 (0.9)
<i>PDGFR</i> exon 18	5 (4.6)
Wild type	3 (2.8)
Unknown	10 (9.3)

*KIT* KIT proto-oncogene receptor tyrosine kinase, *PDGFR* platelet-derived growth factor receptor

No significant change over time was found. The slope was estimated at a negligible  $0.00004 \text{ day}^{-1}$ , with a relative standard error of 25 % ( $P > 0.05$ ).

The median time on imatinib was 27 months (range 1–161). Within the recorded follow-up period, 12 patients treated with palliative intent stopped imatinib because of progressive disease. No statistically significant difference in the TTP was found between patients with low steady-state  $C_{\min}$  values ( $n = 27$ ) and those with adequate  $C_{\min}$  values ( $n = 35$ ) in univariate Cox regression (hazard ratio 1.64, 95 % confidence interval 0.611–5.61;  $P = 0.43$ ) (Fig. 2). In multivariate analysis correcting for the imatinib dose, sex and *KIT* mutational status, the association between the  $C_{\min}$  and TTP remained nonsignificant (hazard ratio 0.60, 95 % confidence interval 0.53–6.35;  $P = 0.34$ ).

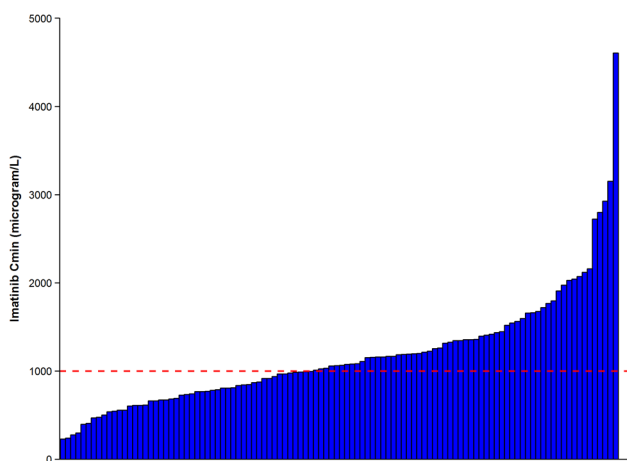
Of the 62 evaluable patients treated with palliative intent, 5 (8.1 %) were non-responders. The median  $C_{\min}$  values were 1270  $\mu\text{g/L}$  in patients showing a radiological response and 920  $\mu\text{g/L}$  in non-responders ( $P = 0.23$ ).

**Table 2** Characteristics of the 421 available plasma imatinib samples

Characteristic	Patients, <i>n</i> = 108
$C_{min}$ [ $\mu\text{g/L}$ ; mean (range)] <sup>a</sup>	1193 (227–4606)
$C_{min}$ category [ <i>n</i> (%)]	
<1000 $\mu\text{g/L}$	48 (44.4)
$\geq 1000$ $\mu\text{g/L}$	60 (55.6)
$C_{min}$ <1000 $\mu\text{g/L}$ in > 75 % of samples [ <i>n</i> (%)]	35 (32.4)
$C_{min}$ $\geq 1000$ $\mu\text{g/L}$ in all samples [ <i>n</i> (%)]	36 (33.3)
Received dose category [ <i>n</i> (%)]	
<400 mg	8 (7.4)
400 mg	86 (79.6)
>400–800 mg	14 (13.0)

$C_{min}$  trough plasma imatinib concentration

<sup>a</sup> Unless specified otherwise, the first representative  $C_{min}$  was used



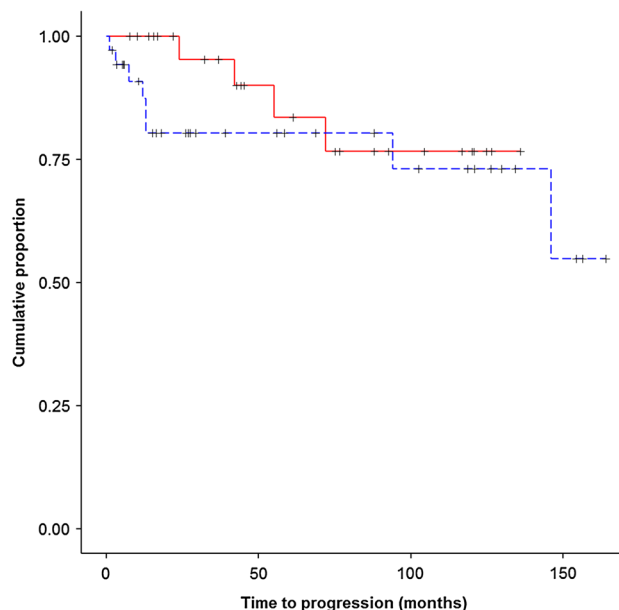
**Fig. 1** Distribution of the 108 patients' first representative trough plasma imatinib concentration ( $C_{min}$ ) values. The dotted red line indicates a  $C_{min}$  of 1000  $\mu\text{g/L}$

(Fig. 3). In the neo-adjuvant setting, no difference in imatinib  $C_{min}$  values was found between responders and non-responders, as all but two patients had a response.

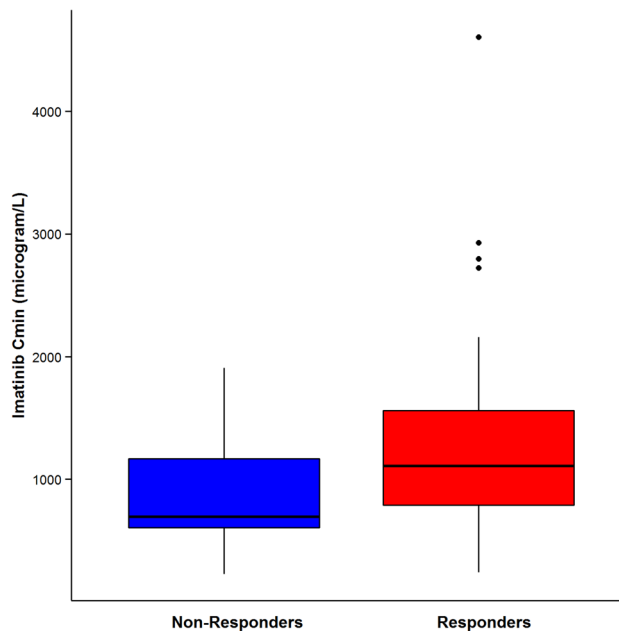
No clinical characteristic (age, type of surgery, sex, extent of resection) was predictive of low imatinib  $C_{min}$  values. Also, no association with tumour characteristics, such as the location ( $P = 0.54$ ), tumour status at registry entry ( $P = 0.23$ ) and mutation status ( $P = 0.48$ ), was found. Four patients (3.7 %) discontinued imatinib treatment because of adverse events. No association with the imatinib  $C_{min}$  was found ( $P = 0.40$ ).

### 4 Discussion

Several studies have linked higher imatinib  $C_{min}$  values to better treatment outcomes [4, 10–13, 15]. In CML, a threshold of  $\geq 1000$   $\mu\text{g/L}$  has been recommended on the basis of several studies [20–22]. In GIST patients, a



**Fig. 2** Time to progression of gastrointestinal stromal tumour patients on imatinib treated with palliative intent as a function of the trough plasma imatinib concentration ( $C_{min}$ ) at steady state. The dashed blue line indicates patients with an imatinib  $C_{min} \geq 1000$   $\mu\text{g/L}$  ( $n = 35$ ), and the solid red line indicates patients with an imatinib  $C_{min} < 1000$   $\mu\text{g/L}$  ( $n = 27$ )



**Fig. 3** Box plot of trough plasma imatinib concentration ( $C_{min}$ ) values measured at steady state in non-responders ( $n = 5$ ) and responders ( $n = 57$ ) to palliative imatinib treatment. The median  $C_{min}$  values were 920  $\mu\text{g/L}$  in non-responders and 1271  $\mu\text{g/L}$  in responders

threshold of  $\geq 1100$   $\mu\text{g/L}$  has been suggested [20–22]. This is based on a study by Demetri et al. [4], in which patients in the lowest  $C_{min}$  quartile (<1100  $\mu\text{g/L}$ ) had a shorter TTP and decreased clinical benefit.

In our cohort, we found that a large proportion of patients were underexposed to imatinib even when a relatively low threshold of  $\geq 1000$   $\mu\text{g/L}$  was used (Table 2; Fig. 1). Although 92.6 % of patients received imatinib doses of 400 mg or higher, >40 % of our patients had imatinib  $C_{\min}$  values  $< 1000$   $\mu\text{g/L}$  in the first steady-state sample, and only one third of patients had adequate  $C_{\min}$  values in every sample (Table 2). This suggests that GIST patients in routine clinical care have a higher risk of underexposure, which may even result in less clinical benefit [4].

The higher average  $C_{\min}$  found by Demetri et al. [4] may have been due to a higher imatinib dose, as patients were randomized to receive either 400 or 600 mg once daily. But other studies in both CML and GIST patients have also described higher concentrations than those observed in our cohort [11, 15]. This could be explained by the fact that those previous studies were performed in a selected and regulated trial setting. In our cohort, no patient selection was made other than the diagnosis of GIST and treatment with imatinib. Although concomitant medication was strictly monitored to prevent possible interactions, no strict exclusion criteria for this study were set considering any concomitant medication causing an interaction for which no replacement was possible. Also, no exclusion criteria were set for comorbidities and laboratory results. Moreover, in routine clinical care, lack of patient compliance could be a factor.

Besides the large percentage of underexposure in the first steady-state sample (relative standard deviation 54 %), we also found a large inpatient variability of 23 %. Only one third of patients had adequate  $C_{\min}$  values in every sample. This is in accordance with the findings reported by Yoo et al. [8], who also found large inter- and inpatient variabilities of 44.7 and 26.5 %, respectively.

An earlier prospective pharmacokinetic study found a significant decrease in systemic exposure to imatinib of almost 30 % within 90 days [9]. The authors hypothesized that this was a consequence of lower oral bioavailability with time, possibly due to upregulation of drug transporters or CYP3A4. Another explanation could be that the decrease in exposure to imatinib resulted from a decrease in  $\alpha 1$ -acid glycoprotein (AGP) as a consequence of the impressive activity of imatinib treatment [23]. In our cohort, the large variability could not be explained by a change in  $C_{\min}$  values over time. A later study also did not find a time-dependent decrease in exposure in a cohort of 65 patients, supporting our finding [24].

No clinical characteristic was found to be predictive of low imatinib  $C_{\min}$  values. Although previous studies have reported lower imatinib  $C_{\min}$  values after major gastrectomy, no correlation between  $C_{\min}$  values and the extent of surgery was found in our study [8].

While previous studies have found a correlation between higher imatinib  $C_{\min}$  values and better clinical outcomes [4, 10–12], our results show that in routine clinical care, underexposure seems to be a substantial issue. Although no statistically significant relationships between exposure to imatinib and treatment response were found, we did find a trend towards responders having higher  $C_{\min}$  values than non-responders in the palliative setting (Fig. 3), and the same trend was found in neo-adjuvant patients. However, no correlation between the  $C_{\min}$  and TTP was found in the palliative subgroup of patients (Fig. 2). This lack of statistically significant differences could have been caused by the small number of non-responders and the limited number of progression events.

Our study gives a new and representative insight into underexposure to imatinib in GIST patients in routine clinical care. We have shown that underexposure is a substantial problem in routine clinical care and that there are large inter- and inpatient variabilities. Given the fact that several studies have described a correlation between  $C_{\min}$  values and response, pharmacokinetically guided dose individualization—also known as therapeutic drug monitoring (TDM)—should be considered. One study attempted to demonstrate the benefits of TDM of imatinib but failed to do so because of small patient numbers and limited physician adherence to TDM recommendations [25].

A prospective clinical trial to assess the benefit of  $C_{\min}$ -guided imatinib dose adjustments in GIST patients is needed. Ideally, such a trial should use a relevant clinical endpoint, such as progression-free survival, because previous studies have found clear correlations between exposure to imatinib and efficacy, and we have now shown that underexposure is a frequent problem in routine clinical care of imatinib-treated GIST patients.

#### Compliance with Ethical Standards

**Funding** A research grant for the Dutch GIST Registry was received from Novartis, Pfizer and Bayer. An unconditional research grant for pharmacokinetic sampling was received from Fonds NutsOhra.

**Conflict of interest** Sheima Farag, Remy Verheijen, Martijn Kerst, Annemiek Cats and Alwin Huitema have no conflicts of interest that are directly relevant to the content of this study. As the principal investigator of the study, Neeltje Steeghs received a research grant from Pfizer, Novartis and Bayer for the Dutch GIST Registry.

#### References

1. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. *Nat Rev Cancer*. 2011;11:865–78.
2. Blanke CD, Rankin C, Demetri GD, Ryan CW, von Mehren M, Benjamin RS, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with



- unresectable or metastatic gastrointestinal stromal tumors expressing the Kit receptor tyrosine kinase: S0033. *J Clin Oncol*. 2008;26:626–32.
3. Patel S, Zalberg JR. Optimizing the dose of imatinib for treatment of gastrointestinal stromal tumours: lessons from the phase 3 trials. *Eur J Cancer*. 2008;44:501–9.
  4. Demetri GD, Wang Y, Wehrle E, Racine A, Nikolova Z, Blanke CD, et al. Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. *J Clin Oncol*. 2009;27:3141–7.
  5. Lankheet NAG, Knapen LM, Schellens JH, Beijnen JH, Steeghs N, Huitema AD. Plasma concentrations of tyrosine kinase inhibitors imatinib, erlotinib, and sunitinib in routine clinical outpatient cancer care. *Ther Drug Monit*. 2014;36(3):326–34.
  6. Peng B, Lloyd P, Schran H. Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet*. 2005;44:879–94.
  7. Eechoute K, Sparreboom A, Burger H, Franke RM, Schiavon G, Verweij J, et al. Drug transporters and imatinib treatment: implications for clinical practice. *Clin Cancer Res*. 2011;17:406–15.
  8. Yoo C, Ryu M-H, Kang BW, Yoon S-K, Ryoo B-Y, Chang H-M, et al. Cross-sectional study of imatinib plasma trough levels in patients with advanced gastrointestinal stromal tumors: impact of gastrointestinal resection on exposure to imatinib. *J Clin Oncol*. 2010;28:1554–9.
  9. Eechoute K, Fransson MN, Reyners AK, de Jong FA, Sparreboom A, van der Graaf WT, et al. A long-term prospective population pharmacokinetic study on imatinib plasma concentrations in GIST patients. *Clin Cancer Res*. 2012;18:5780–7.
  10. Delbaldo C, Chatelut E, Ré M, Deroussent A, Séronie-Vivien S, Jambu A, et al. Pharmacokinetic–pharmacodynamic relationships of imatinib and its main metabolite in patients with advanced gastrointestinal stromal tumors. *Clin Cancer Res*. 2006;12:6073–8.
  11. von Mehren M, Widmer N. Correlations between imatinib pharmacokinetics, pharmacodynamics, adherence, and clinical response in advanced metastatic gastrointestinal stromal tumor (GIST): an emerging role for drug blood level testing? *Cancer Treat Rev*. 2011;37:291–9.
  12. Widmer N, Decosterd LA, Csajka C, Montemurro M, Haouala A, Leyvraz S, et al. Imatinib plasma levels: correlation with clinical benefit in GIST patients. *Br J Cancer*. 2010;102:1198–9.
  13. Picard S, Titier K, Etienne G, Teilhet E, Ducint D, Lassalle R, et al. Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia. *Blood*. 2007;109:3496–9.
  14. Singh N, Kumar L, Meena R, Velpandian T. Drug monitoring of imatinib levels in patients undergoing therapy for chronic myeloid leukaemia: comparing plasma levels of responders and non-responders. *Eur J Clin Pharmacol*. 2009;65:545–9.
  15. Larson RA, Druker BJ, Guilhot F, O'Brien SG, Riviere GJ, Krahnke T, et al. Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study. *Blood*. 2008;111:4022–8.
  16. Lankheet NAG, Hillebrand MJX, Rosing H, Schellens JHM, Beijnen JH, Huitema ADR. Method development and validation for the quantification of dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, sorafenib and sunitinib in human plasma by liquid chromatography coupled with tandem mass spectrometry. *Biomed Chromatogr*. 2013;27:466–76.
  17. Wang Y, Chia YL, Nedelman J, Schran H. A therapeutic drug monitoring algorithm for refining the imatinib trough level obtained at different sampling times. *Ther Drug Monit*. 2009;31:579–84.
  18. Takahashi N, Wakita H, Miura M, Scott SA, Nishii K, Masuko M, et al. Correlation between imatinib pharmacokinetics and clinical response in Japanese patients with chronic-phase chronic myeloid leukemia. *Clin Pharmacol Ther*. 2010;88:809–13.
  19. R Development Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2008.
  20. Teng T, Mabasa VH, Mary H, Ensom H, Pharm BS. The role of therapeutic drug monitoring of imatinib in patients with chronic myeloid leukemia and metastatic or unresectable gastrointestinal stromal tumors. *Ther Drug Monit*. 2012;34:85–97.
  21. Yu H, Steeghs N, Nijenhuis CM, Schellens JHM, Beijnen JH, Huitema ADR. Practical guidelines for therapeutic drug monitoring of anticancer tyrosine kinase inhibitors: focus on the pharmacokinetic targets. *Clin Pharmacokinet*. 2014;53:305–25.
  22. de Wit D, Guchelaar H-J, den Hartigh J, Gelderblom H, van Erp NP. Individualized dosing of tyrosine kinase inhibitors: are we there yet? *Drug Discov Today*. 2015;20:18–36.
  23. Chatelut E, Gandia P, Gotta V, Widmer N. Long-term prospective population PK study in GIST patients [letter]. *Clin Cancer Res*. 2013;19:949.
  24. Yoo C, Ryu M-H, Ryoo B-Y, Beck MY, Chang H-M, Lee J-L, et al. Changes in imatinib plasma trough level during long-term treatment of patients with advanced gastrointestinal stromal tumors: correlation between changes in covariates and imatinib exposure. *Invest New Drugs*. 2012;30:1703–8.
  25. Gotta V, Widmer N, Decosterd LA, Chalandon Y, Heim D, Gregor M, et al. Clinical usefulness of therapeutic concentration monitoring for imatinib dosage individualization: results from a randomized controlled trial. *Cancer Chemother Pharmacol*. 2014;74:1307–19.