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SHORT REPORT

# 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

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**Summary** A pharmacokinetic study in patients with gastrointestinal stromal tumors (GIST) suggested that imatinib plasma concentration may decrease following long-term exposure. We assessed changes in imatinib plasma trough levels ($C_{min}$) during long-term treatment. Follow-up (FU) imatinib $C_{min}$ was measured in 65 patients who received the same dose of imatinib for at least 9 months after previous (initial) tests. After exclusion of 7 patients who had been treated with imatinib for over 2 years at the time of initial testing, 58 patients were included in this analysis. The median intervals from initiation of imatinib to initial testing and from initial to FU testing were 5.5 months (range, 0.5–24.0 months) and 13.0 months (range, 9.6–17.9 months), respectively. Mean inter- and intra-subject variability values were 47.7% and 20.9%, respectively, at initial measurements, and 45.2% and 19.4%, respectively, at FU. Mean FU imatinib $C_{min}$ (1,370±661 ng/mL) was significantly higher than mean initial $C_{min}$ (1,171±573 ng/mL; $p$=0.003). Compared with initial $C_{min}$, FU $C_{min}$ was decreased in 22 patients and increased in 36, with median changes of 13% and 32%, respectively. Multivariate analysis showed a significant correlation between the ratio of FU to initial imatinib $C_{min}$ and that of albumin ($r$=−0.39, $p$=0.003). During long-term treatment, imatinib $C_{min}$ did not decrease significantly but remained stable or increased in most patients. Changes in imatinib $C_{min}$ were associated with changes in albumin concentration. Monitoring of imatinib $C_{min}$ only for concerns about time-dependent increases in imatinib clearance is not necessary.

**Keywords** Pharmacokinetics · Imatinib · Gastrointestinal stromal tumor

## Introduction

Imatinib mesylate (Glivec®/Gleevec®/Imatinib, Novartis Oncology, East Hanover, NJ) is an orally bioavailable tyrosine kinase inhibitor that acts on BCR-ABL, as well as the DDR, KIT, and PDGFR kinases [1–3]. Imatinib has markedly improved survival outcomes and become a treatment of choice in patients with advanced, unresectable gastrointestinal stromal tumors (GIST) [4–7]. The standard dose of imatinib is 400 mg once daily, but an increase to 800 mg/day has shown additional clinical benefits in patients with disease progression on 400 mg/day [8–10].

Imatinib is rapidly and almost completely (98%) absorbed from the gastrointestinal tract, with most (>95%) binding to plasma proteins such as albumin and $\alpha_1$-acid glycoprotein (AGP) [11]. Imatinib is metabolized by cytochrome P450 (CYP) enzymes, primarily CYP 3A4 and 3A5, with a number of influx and efflux transporters thought to be responsible for intracellular drug concentration [11]. Pharmacokinetic (PK) studies in patients with

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chronic myeloid leukemia (CML) and GIST have found that variables significantly affecting or associated with the plasma concentration of imatinib include white blood cell (WBC) and granulocyte counts; hemoglobin and AGP concentrations; age; body weight and body surface area (BSA); and previous major gastrectomy (i.e., subtotal or total gastrectomy) [12–17].

Satisfactory clinical outcomes in patients with CML and GIST require sufficient exposure to imatinib [18–20]. In patients with GIST, imatinib plasma trough concentrations ($C_{min}$) greater than 1,100 ng/mL were correlated with higher rates of objective response and longer progression-free survival [20].

An early population PK study of patients with GIST showed that imatinib clearance was 33% higher after about 12 months of therapy than on day 1, suggesting that exposure to imatinib decreases with extended administration [12]. If this is true, since median progression in GIST patients during first line treatment with imatinib occurs at about 2 years [6, 8], disease progression in patients initially controlled on imatinib may be at least in some patients due to a gradual decrease in imatinib exposure over time. Moreover, frequent monitoring of plasma imatinib concentration and fine tuning of imatinib dosage may be necessary to maintain the long-term effects of imatinib. In a previous study, however, we did not observe a correlation between duration of exposure to imatinib and imatinib $C_{min}$ [16]. Because that study was limited by its cross-sectional design, we assessed changes in imatinib $C_{min}$ during long-term exposure.

## Materials and methods

### Patients

Since October 2008, steady-state imatinib $C_{min}$ has been measured in patients ≥18 years of age at Asan Medical Center, Seoul, Korea, with histologically and/or molecularly documented GIST, who showed good compliance and were treated for at least 2 weeks with a constant dose of imatinib. Of patients whose plasma concentration of imatinib had been measured (initial PK tests), we selected those who received the same dose of imatinib for at least 9 months and performed follow-up (FU) measurements of plasma imatinib concentration. Patients with any serious comorbidity or who were administered any concomitant medications that could inhibit or induce CYP 3A enzymes were excluded. Before the initial and FU PK measurements, patients were asked to take the same dose of imatinib at a fixed time for at least 7 days and to keep a drug-use diary. Patients who did not comply with this request were rescheduled for PK tests. Body weight, body surface area (BSA), complete blood counts, serum chemistry and serum creatinine concentration were measured within 7 days of each PK assessment. Creatinine clearance was estimated using the Cockcroft-Gault formula: estimated creatinine clearance = (140-age) × (weight in kilograms) × (0.85 if female)/(72 × serum creatinine) [21]. Patient medical records were retrospectively reviewed to collect clinico-pathologic data. The study protocol was approved by the Institutional Review Board of the Asan Medical Center, and all patients provided written informed consent.

### PK data collection

Within 22–26 h after the previous dose of imatinib, blood samples (at least 4 mL) were collected into heparinized tubes, centrifuged at 3,000 rpm for 10 min at room temperature and stored at −20°C within 1 h of collection. Plasma concentrations of imatinib were measured by liquid chromatography-tandem mass spectrometry at the Seoul Clinical Laboratories (Seoul, Korea), with the kind support of Novartis Korea [22]. Two measurements of imatinib $C_{min}$ were obtained on two different days, with the average value used for analysis; if, however, imatinib $C_{min}$ was measured once, that value was used.

### Statistical analysis

Imatinib $C_{min}$ was dose-adjusted and log-transformed. The Wilcoxon rank test was used to compare the means of initial and FU imatinib $C_{min}$, and one sample *t*-tests were performed to determine whether initial and FU imatinib $C_{min}$ differed within each individual patient. Linear regression analysis was used to compare the ratios of FU to initial imatinib $C_{min}$ (FU: initial) with covariates to find correlative factors for changes in imatinib $C_{min}$ over time. In per-sample analysis, the correlations between imatinib $C_{min}$ and covariates, such as age, sex, body weight, BSA, duration of imatinib treatment, hemoglobin concentration, WBC, absolute neutrophil count (ANC), platelet count, albumin concentration, creatinine clearance and previous major gastrectomy, were analyzed using linear regression. Potential correlative covariates with $p<0.2$ in univariate analyses were assessed in multivariate analysis using a multiple linear regression model. All tests were two-sided and a *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Patient characteristics

Between November 2009 and May 2010, 65 patients who met the inclusion criteria were enrolled. Seven patients who

had been treated with imatinib for over 2 years (range, 29–67 months) at the time of initial PK testing were excluded because of potential confounding effects on time-dependent PK changes. From the remaining 58 patients, $C_{min}$ was initially measured in 114 blood samples between October 2008 and May 2009 and at FU, $C_{min}$ was measured in 104 blood samples.

Baseline characteristics of the 58 included patients are shown in Table 1. Median patient age was 53 years (range, 28–76 years) and 37 (63.8%) patients were male. Seventeen (29.3%) patients received imatinib as adjuvant therapy after curative resection, whereas 41 (70.7%) received imatinib as primary therapy for unresectable or metastatic disease. Fifty-four (93.1%) patients were treated with 400 mg/day and 4 (6.9%) with 300 mg/day imatinib. The median time from initiation of imatinib to initial PK testing was 5.5 months (range, 0.5–24.0 months), the median time between initial and FU PK testing was 13.0 months (range, 9.6–17.9 months), and the median time from initiation of imatinib to FU PK testing was 19.4 months (range, 11.6–38.8 months).

**Table 1** Baseline clinicopathologic characteristics

| Characteristics | Patients ($n$=58) |
|---|---|
| Sex, *n* (%) | |
| Male | 37 (63.8) |
| Female | 21 (36.2) |
| Age (years), median (range) | 53 (28–76) |
| C-kit overexpression, *n* (%) | 57 (98.3) |
| Kinase mutations, *n* (%) | |
| *KIT* exon 11 | 33 (56.9) |
| *KIT* exon 9 | 5 (8.6) |
| PDGFRA 12 | 3 (5.2) |
| PDGFRA 18 | 1 (1.7) |
| Wild type | 12 (20.7) |
| Unknown | 4 (6.9) |
| Primary site, *n* (%) | |
| Stomach | 28 (48.3) |
| Small bowel | 24 (41.4) |
| Peritoneum | 4 (6.9) |
| Others | 2 (3.4) |
| Imatinib dose, *n* (%) | |
| 400 mg/day | 54 (93.1) |
| 300 mg/day | 4 (6.9) |
| Previous major gastrectomy, *n* (%) | |
| No | 44 (75.9) |
| Yes | 14 (24.1) |
| Treatment duration of imatinib before initial plasma level test (months), median (range) | 5.5 (0.5–24.0) |

## Imatinib $C_{min}$ at initial and FU PK testing

We found that the FU mean ± standard deviation (SD) imatinib $C_{min}$ (1,370±661 ng/mL) was significantly higher than the mean ± SD initial $C_{min}$ (1,171±573 ng/mL; $p$=0.003; Fig. 1). The distribution of FU:initial imatinib $C_{min}$ ratios, representing individual changes in imatinib $C_{min}$ over time, is presented in Fig. 2. The median (range) of FU:initial imatinib $C_{min}$ ratios was 1.14 (0.50–3.35), indicating that imatinib $C_{min}$ was a median 14% higher at FU than initially ($p$=0.001). When compared with initial $C_{min}$, FU $C_{min}$ was lower in 22 (38%) patients and higher in 36 (62%), with median changes of 13% and 32%, respectively. The absolute change from initial to FU $C_{min}$ was ≤30% in 35 patients, >30% to ≤60% in 14 patients, and >60% in 9 patients. The mean inter- and intra-subject variabilities were 47.7% and 20.9%, respectively, at initial measurement and 45.2% and 19.4%, respectively, at FU.

## Covariates associated with changes in imatinib $C_{min}$ over time

To investigate the covariates correlating with changes in imatinib $C_{min}$ over time, we compared FU:initial ratios of covariates and imatinib $C_{min}$. Univariate analysis showed that the FU:initial ratios of hemoglobin ($p$=0.02) and albumin ($p$<0.001) concentrations were inversely correlated with those of imatinib $C_{min}$ (Fig. 3 and Table 2). However, we observed no correlation between the FU:initial ratios of imatinib $C_{min}$ and other variables, such as BSA, platelet count, ANC, creatinine clearance and time from initiation of imatinib treatment to initial PK testing. In multivariate analysis, only changes in albumin concentration were

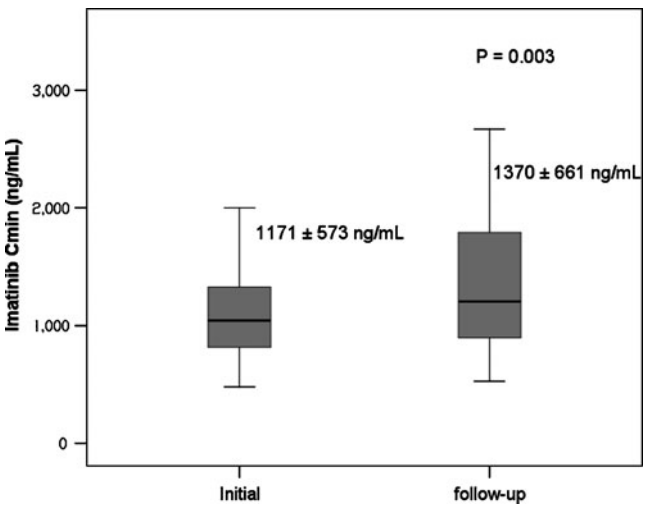


**Fig. 1** Initial and follow-up imatinib $C_{min}$, reported as mean ± standard deviation

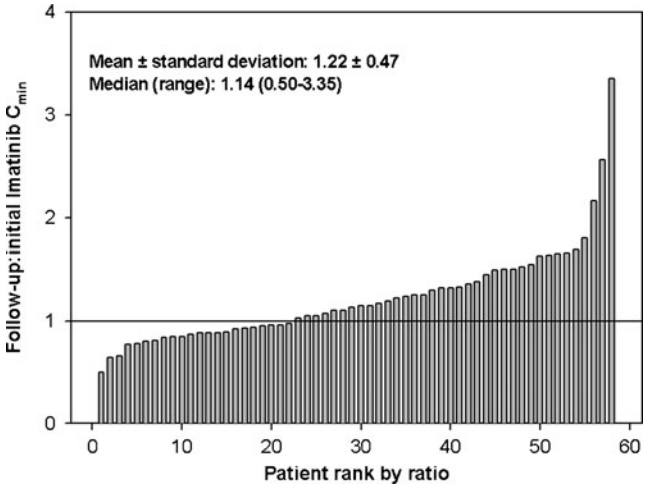


**Fig. 2** Ratios of follow-up to initial imatinib $C_{min}$

significantly correlated with changes in imatinib $C_{min}$ (Table 2).

Per-sample analysis of imatinib $C_{min}$

Per-sample PK analysis showed that age, BSA, hemoglobin and albumin concentrations, creatinine clearance, and previous major gastrectomy were associated with imatinib $C_{min}$ in a univariate linear regression model. In multivariate analysis, hemoglobin concentration, creatinine clearance, and previous major gastrectomy remained significant, independent covariates associated with imatinib $C_{min}$ (Table 3). In contrast, duration of treatment with imatinib before measurement of plasma imatinib concentration was not associated with imatinib $C_{min}$ ($p$=0.55).

## Discussion

We have shown here that imatinib $C_{min}$ did not decrease significantly over time in most patients with GIST. When compared with $C_{min}$ measurements performed at a median 5.5 months after initiation of imatinib, $C_{min}$ measurements after a median 13 months of further treatment increased in about 50% of patients. Since the median increase was only 14%, however, it may not be clinically meaningful, being due to the large intra-patient variability. Therefore, our results suggest that, in patients on long-term, chronic imatinib therapy, steady-state imatinib $C_{min}$ remains stable over time without significantly declining. Although this finding may conflict with previous results, which showed a time-dependent decrease in imatinib PK levels [12], differences in study design and PK parameters make it difficult to directly compare these results with ours. The strength of the earlier study was that it measured all major PK parameters at fixed time points (day 1, day 29 and after 1 year) [12]. PK results at days 1 and 29 were drawn from sufficient patients to allow conclusions to be drawn regarding the potential effects of changes in activities of metabolizing enzymes and plasma binding proteins during the early course of imatinib treatment. However, PK tests after 1 year of imatinib treatment were performed in only about half of initially enrolled patients. This may have limited the ability of these data to show changes in imatinib PK in GIST patients receiving long-term treatment. In contrast to that study, we assessed $C_{min}$ data at two time points (initial and FU) in all of our patients, allowing us to determine both overall and individual changes in imatinib $C_{min}$. Because initial PK was measured at a median 5.5 months after initiation of imatinib therapy, adjustments in metabolizing enzyme activity and plasma binding proteins may already have occurred in most of our patients at the time of first PK sampling. Thus, our initial PK measurements likely reflect the status of patients after chronic exposure to imatinib. Accordingly, our results indicate that imatinib plasma levels remained stable during

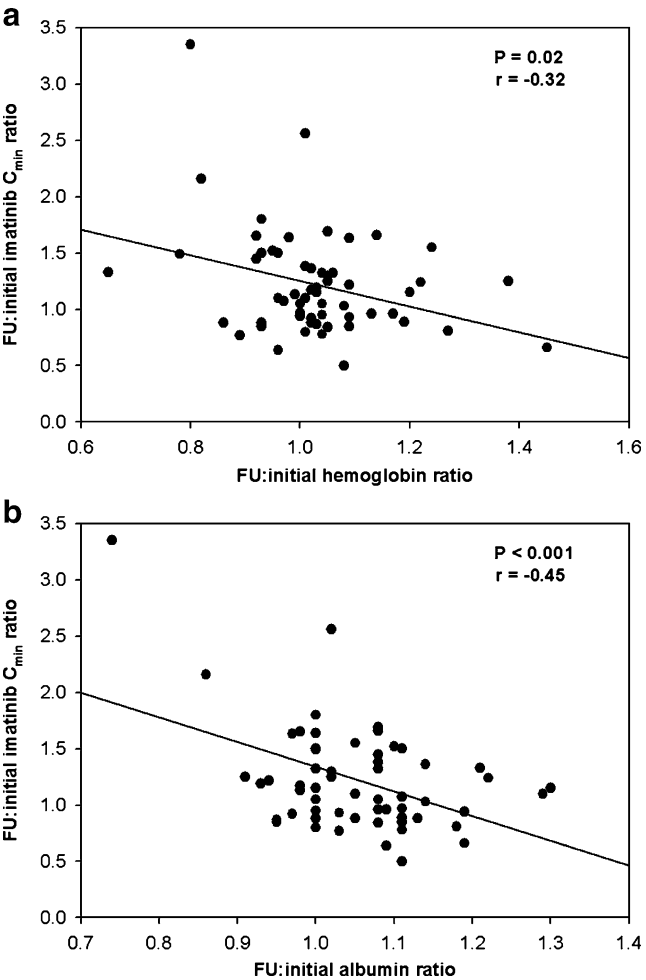


**Fig. 3** Correlation between follow-up (FU):initial imatinib $C_{min}$ ratio and FU:initial ratios of hemoglobin and albumin

**Table 2** Correlation between follow-up/initial ratios of imatinib $C_{min}$ and covariates

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | Correlation coefficient | *p*-value | Correlation coefficient | *p*-value |
| FU:initial hemoglobin ratio | −0.32 | 0.02 | −0.21 | 0.15 |
| FU:initial WBC ratio | −0.20 | 0.13 | −0.01 | 0.95 |
| FU:initial albumin ratio | −0.45 | <0.001 | −0.39 | 0.003 |

*FU* follow-up; *WBC* white blood cell

long-term treatment in most patients, not during the early stage of treatment. In addition, the median 19 months of imatinib therapy at FU PK testing in the present study seems sufficient to test the hypothesis that secondary imatinib resistance, which occurs around a median 2 years of imatinib treatment, may be the result of a reduction in imatinib levels [23, 24].

We performed additional subgroup analyses according to time from initiation of imatinib to initial PK testing (<3 months vs 3–12 months vs >12 months) and from initial to FU PK testing (9–12 months vs >12 months). In each group, mean FU $C_{min}$ was not lower than initial $C_{min}$. Moreover, there were no between group differences in the numbers of patients with decreased $C_{min}$, although these findings were not conclusive due to the small number of patients in each group (data not shown).

Although treatment with imatinib has remarkably improved clinical outcomes of patients with GIST, over half of these patients show disease progression within 2 years [6, 8]. There have been concerns that tumor progression may be due to suboptimal exposure to imatinib during long-term treatment. Clinically, however, our results suggest that decreased exposure to imatinib due to increased clearance is not a major cause of disease progression in these patients on long-term treatment. Rather, disease progression during chronic treatment is more likely due to acquired resistance including secondary gene mutations [24]. Therefore, our findings indicate that monitoring of imatinib $C_{min}$ is not required unless patients appear to be exposed beyond the appropriate range, such as non-compliance, unusual severe adverse events, or initiation or discontinuation of concomitant medications that considerably affect the activity of CYP 3A enzymes.

Drug exposure to imatinib during treatment may be affected by various factors, especially by changes in covariates. We found that changes in albumin were significantly and inversely associated with changes in imatinib $C_{min}$ [16, 20]. This finding suggests that increased imatinib $C_{min}$ might be associated with decreased albumin concentration, which could be affected by various clinical occurrences, rather than a real decline in imatinib clearance. Changes in other variables, such as hemoglobin concentration, WBC, creatinine clearance and treatment duration, did not correlate with changes in imatinib $C_{min}$.

Although it was not a primary objective of this study, we performed per-sample analysis to verify the covariates correlated with imatinib $C_{min}$ in this patient population. Our results were consistent with those of previous studies, which found that hemoglobin concentration, creatinine clearance and previous major gastrectomy were significantly associated with imatinib $C_{min}$ [12–17]. Our finding on the association between major gastrectomy and imatinib $C_{min}$ is in good agreement with previous results on the impact of anatomical defects in the stomach on exposure to imatinib [16]. This result, however, requires further validation, because 47 (81.0%) patients in this study were included in the previous study [16].

Other factors may also affect exposure to imatinib. Because imatinib is metabolized primarily by CYP 3A enzymes and in the blood, and is bound to AGP as well as to albumin [11], variations in CYP 3A activities and AGP

**Table 3** Per-sample analysis for correlation with imatinib $C_{min}$

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | Correlation coefficient | *p*-value | Correlation coefficient | *p*-value |
| Age | 0.20 | 0.03 | −0.19 | 0.12 |
| BSA | −0.20 | 0.03 | 0.06 | 0.65 |
| Hemoglobin | −0.34 | <0.001 | −0.25 | 0.02 |
| WBC | −0.17 | 0.06 | −0.07 | 0.45 |
| Platelet | −0.15 | 0.12 | −0.09 | 0.34 |
| Albumin | −0.29 | 0.002 | −0.15 | 0.11 |
| Creatinine clearance | −0.36 | <0.001 | −0.38 | 0.01 |
| Previous major gastrectomy | −0.22 | 0.02 | −0.30 | 0.002 |

*BSA* body surface area; *WBC* white blood cell

concentrations may affect imatinib $C_{min}$. Therefore, our lack of data on CYP 3A enzymes and AGP limits our ability to explain the variation in imatinib $C_{min}$. Although we measured only $C_{min}$, because $C_{min}$ of imatinib in patients with GIST has been shown to be highly correlated with peak concentration ($C_{max}$) and area under the plasma concentration-time curve (AUC), it may not limit our findings in the present study [20].

In conclusion, steady-state imatinib $C_{min}$ did not decrease significantly but remained stable or increased slightly in most patients during long-term treatment. Changes in imatinib $C_{min}$ were correlated with changes in serum albumin concentration. Monitoring of imatinib $C_{min}$ only due to concerns about time-dependent increased clearance of imatinib is not necessary.

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**Conflicts of interest** Yoon-Koo Kang: Honorarium and consultant for Novartis and Pfizer

## References

1. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ (2000) Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. Blood 96(3):925–932
2. Buchdunger E, Cioffi CL, Law N, Stover D, Ohno-Jones S, Druker BJ et al (2000) Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther 295(1):139–145
3. Day E, Waters B, Spiegel K, Alnadaf T, Manley PW, Buchdunger E et al (2008) Inhibition of collagen-induced discoidin domain receptor 1 and 2 activation by imatinib, nilotinib and dasatinib. Eur J Pharmacol 599(1–3):44–53
4. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ et al (2002) Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 347(7):472–480
5. Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY et al (2004) Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 364(9440):1127–1134
6. Blanke CD, Rankin C, Demetri GD, Ryan CW, von Mehren M, Benjamin RS et al (2008) 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 26(4):626–632
7. Ryu MH, Kang WK, Bang YJ, Lee KH, Shin DB, Ryoo BY et al (2009) A prospective, multicenter, phase 2 study of imatinib mesylate in Korean patients with metastatic or unresectable gastrointestinal stromal tumor. Oncology 76(5):326–332
8. Blanke CD, Demetri GD, von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA et al (2008) Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 26(4):620–625
9. Debiec-Rychter M, Sciot R, Le Cesne A, Schlemmer M, Hohenberger P, van Oosterom AT et al (2006) KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 42(8):1093–1103
10. Park I, Ryu MH, Sym SJ, Lee SS, Jang G, Kim TW et al (2009) Dose escalation of imatinib after failure of standard dose in Korean patients with metastatic or unresectable gastrointestinal stromal tumor. Jpn J Clin Oncol 39(2):105–110
11. Peng B, Lloyd P, Schran H (2005) Clinical pharmacokinetics of imatinib. Clin Pharmacokinet 44(9):879–894
12. Judson I, Ma P, Peng B, Verweij J, Racine A, di Paola ED et al (2005) Imatinib pharmacokinetics in patients with gastrointestinal stromal tumour: a retrospective population pharmacokinetic study over time. EORTC Soft Tissue and Bone Sarcoma Group. Cancer Chemother Pharmacol 55(4):379–386. doi:10.1007/s00280-004-0876-0
13. Delbaldo C, Chatelut E, Re M, Deroussent A, Seronie-Vivien S, Jambu A et al (2006) Pharmacokinetic-pharmacodynamic relationships of imatinib and its main metabolite in patients with advanced gastrointestinal stromal tumors. Clin Cancer Res 12(20 Pt 1):6073–6078
14. Menon-Andersen D, Mondick JT, Jayaraman B, Thompson PA, Blaney SM, Bernstein M et al (2009) Population pharmacokinetics of imatinib mesylate and its metabolite in children and young adults. Cancer Chemother Pharmacol 63(2):229–238. doi:10.1007/s00280-008-0730-x
15. Schmidli H, Peng B, Riviere GJ, Capdeville R, Hensley M, Gathmann I et al (2005) Population pharmacokinetics of imatinib mesylate in patients with chronic-phase chronic myeloid leukaemia: results of a phase III study. Br J Clin Pharmacol 60(1):35–44
16. Yoo C, Ryu MH, Kang BW, Yoon SK, Ryoo BY, Chang HM et al (2010) 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 28 (9):1554–1559
17. Widmer N, Decosterd LA, Csajka C, Leyvraz S, Duchosal MA, Rosselet A et al (2006) Population pharmacokinetics of imatinib and the role of alpha-acid glycoprotein. Br J Clin Pharmacol 62(1):97–112
18. Larson RA, Druker BJ, Guilhot F, O'Brien SG, Riviere GJ, Krahnke T et al (2008) Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study. Blood 111(8):4022–4028
19. Picard S, Titier K, Etienne G, Teilhet E, Ducint D, Bernard MA et al (2007) Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia. Blood 109(8):3496–3499
20. Demetri GD, Wang Y, Wehrle E, Racine A, Nikolova Z, Blanke CD et al (2009) Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. J Clin Oncol 27(19):3141–3147
21. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16(1):31–41
22. Bakhtiar R, Lohne J, Ramos L, Khemani L, Hayes M, Tse F (2002) High-throughput quantification of the anti-leukemia drug STI571 (Gleevec) and its main metabolite (CGP 74588) in human plasma using liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 768(2):325–340
23. Wardelmann E, Merkelbach-Bruse S, Pauls K, Thomas N, Schildhaus HU, Heinicke T et al (2006) Polyclonal evolution of multiple secondary KIT mutations in gastrointestinal stromal tumors under treatment with imatinib mesylate. Clin Cancer Res 12(6):1743–1749
24. Antonescu CR, Besmer P, Guo T, Arkun K, Hom G, Koryotowski B et al (2005) Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. Clin Cancer Res 11(11):4182–4190