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ORIGINAL ARTICLE

Nilotinib in patients with GIST who failed imatinib and sunitinib: importance of prior surgery on drug bioavailability

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Abstract
Purpose To evaluate the efficacy of nilotinib in patients with advanced gastrointestinal stromal tumors (GISTs) resistant or intolerant to both imatinib and sunitinib and to explore the potential relationship between nilotinib pharmacokinetics and clinical outcomes.
Patients and methods We analyzed the efficacy, tolerability and pharmacokinetic parameters of nilotinib (400 mg twice daily) in 17 GIST patients with histories of prior gastrointestinal surgery.
Results Median patient age was 59 years (range, 35–71 years), 14 of 17 patients (82.4%) were male, and mean body weight was 59.4 kg. Of the 17 patients, 2 (11.8%) had partial responses (PR), 10 (58.8%) had stable disease (SD), and 5 (29.4%) had progressive disease (PD), with a clinical benefit rate (CR + PR + SD) at 24 weeks of 47.0%. Median progression-free survival (PFS) and overall survival (OS) were 23.6 weeks (95% confidence interval [CI] 0.0–50.6 weeks) and 74.0 weeks (95% CI 27.4–120.6 weeks), respectively. Most observed adverse events were mild (grade 1, 41.2%; grade 2, 52.9%), with no grade 3/4 events. Pharmacokinetic parameters of nilotinib were as follows: C_{max} of 1,754 ± 970 μg/L, $T_{1/2}$ of 13.4 ± 8.94 h and $AUC_{0-12\ h}$ of 14,190 ± 6,853 h μg/L. The $AUC_{0-12\ h}$ of nilotinib was significantly lower in the 4 patients with prior major (total or subtotal) gastrectomy than in the other 13 patients (8,526 ± 7,869 h μg/L vs. 15,930 ± 5,759 h μg/L, $P = 0.014$). Of the 4 gastrectomized patients, two (50%) showed markedly decreased nilotinib exposure ($AUC_{0-12\ h}$ of 1,914 and 3,194 h μg/L) and rapid disease progression (PFS of 4.6 and 7.1 weeks).
Conclusion Nilotinib was active and safe in patients with advanced GIST resistant to both imatinib and sunitinib. Major gastrectomy decreased the bioavailability of nilotinib and, in some patients, lowered its clinical activity.

Keywords Pharmacokinetics · Nilotinib · Gastrointestinal stromal tumor · Gastrectomy

Introduction

Tyrosine kinase inhibitors (TKI) have revolutionized the treatment of gastrointestinal stromal tumors (GISTs). Imatinib (Glivec®/Gleevec®; Novartis) and sunitinib (Sutene®; Pfizer) are now established as first- and second-line TKIs, respectively, for patients with advanced GIST, with both showing high tumor control rates [1–5]. Most patients, however, develop resistance to imatinib and sunitinib, at a median 24 and 12 months, respectively [6–8]. Therefore, there is an urgent need for optimized use of imatinib and sunitinib, e.g. based on pharmacokinetics, or for newer or more potent agents without having cross-resistance with either.

Nilotinib (Tasigna®; Novartis) is a new TKI that inhibits BCR-ABL, as well as the receptor kinases for stem cell factor (KIT), PDGFR-α, PDGFR-ß and collagen (DDR-1/DDR-2) [9]. Due to differences in cellular transporters, the intracellular concentrations of nilotinib may be tenfold higher than those of imatinib, which may be reflected by

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the clinical efficacy of nilotinib in patients with chronic myeloid leukemia (CML) resistant or intolerant to prior therapy that included imatinib [10, 11]. Recently, nilotinib has been reported to be active in patients with GIST who progressed or failed prior therapy with imatinib and sunitinib [12, 13].

Nilotinib is formulated as 200 mg hard capsules for oral administration and is under investigation as 400 mg twice daily in patients with GIST. The solubility of this formulation in aqueous solution decreases with increasing pH, becoming insoluble in phosphate buffers of pH higher than 4.5. In clinical trials evaluating the absorption of nilotinib, solubility has been limiting in doses above 400 mg and high-fat meals have increased the bioavailability of nilotinib in CML patients and healthy volunteers [14].

GIST patients on oral TKIs often have altered gastrointestinal tract physiology due to the disease itself and/or related surgical managements. While surgery is the treatment of choice for patients with localized GIST, patients with metastatic or recurrent GIST also receive surgical interventions to debulk residual disease or focal progressive lesions and to control localized complications, including hemorrhage and perforation. Recently, we observed that the trough plasma concentrations of imatinib, which has acid-dependent solubility, were significantly lower in gastrectomized than in non-gastrectomized patients [15]. The objectives of this study was to evaluated the pharmacokinetic effects of gastrectomy or small intestine resection on nilotinib, whose solubility is also influenced by acidity, in patients participating in the Compassionate Use Program. We additionally assessed the efficacy and tolerability of nilotinib in patients with advanced GISTs resistant to both imatinib and sunitinib and compared the effects of prior gastrointestinal resections.

Materials and methods

Patient selection

This study included patients with GIST who participated in the Compassionate Use Program for nilotinib at the Asan Medical Center, Seoul, Korea, between May 2007 and October 2009. Inclusion criteria included histologically documented advanced GIST, failure (progression or intolerance) to both imatinib and sunitinib, age $\geq$15 years, WHO performance score $\leq$2, and adequate organ and bone marrow function. Patients were excluded if they received any QT-prolonging medication or CYP3A4 inhibitors, had any serious comorbidity, or if oral administration was restricted due to significant gastrointestinal bleeding or obstruction.

Treatment schedule

Nilotinib was started and maintained at 400 mg bid; two 200 mg capsules were swallowed with water 2 h or more after food ingestion at about 10 AM and 10 PM every day.

Treatment assessment

Safety was assessed by history taking, physical examination, WHO performance status, hematology and serum biochemistry, performed every 2 weeks for the first month of treatment and every month thereafter. Adverse events were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Tumor assessments by abdominopelvic dynamic CT imaging were performed every 4 weeks for the first 2 months and every 8 weeks thereafter. Best overall response was assessed according to the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.0 with some modifications. Despite their increased size, lesions showing necrosis were not considered progressive disease, nor were new cystic lesions in the liver [16–18]. The primary efficacy parameter was the best overall tumor response based on RECIST. Secondary efficacy parameters included progression-free survival (PFS), overall survival (OS) and clinical benefit rate (complete response [CR] + partial response [PR] + stable disease [SD]) at 24 weeks. PFS was measured from the date of nilotinib initiation to the date of documented progression or death, whatever the cause. Patients who were alive and progression free were censored at the date of last follow-up. OS was measured from the date of nilotinib initiation to the date of death, whatever the cause. Patients alive at the time of analysis were censored at date of last follow-up. If pretreatment GIST biopsy samples were available, their genomic DNA was analyzed for mutations in exons 9, 11, 13 and 17 of *KIT* and exons 12 and 18 of *PDGFRA* [18].

Pharmacokinetics

Pharmacokinetic parameters were measured after patients had taken, and complied with, nilotinib 400 mg twice daily for at least 4 weeks. Blood samples (3 ml each) for the determination of steady state serum concentrations of nilotinib were taken 0 (predose), 1, 2, 3, 5, 8 and 12 h after, the morning dose of nilotinib. Within 60 min of drawing, each whole blood sample was centrifuged at about 5°C for 10 min at approximately 1,100 g. Each serum sample (about 1.5 mL) was transferred to a 2-mL polypropylene screw-cap tube and stored at ≤ -20°C. All samples were shipped to the analytical site for analyses by Novartis Pharmaceuticals Corporation. Serum concentration data

were analyzed by standard non-compartmental methods using WINNonlin version 5.1 (Pharsight Corp, Mountain View, CA).

Statistical analysis

Descriptive statistics were used for pharmacokinetic parameters. The PFS and OS were estimated using the Kaplan–Meier method. We also evaluated the effects of prior major (total or subtotal) gastrectomy or small intestinal resection on the efficacy and pharmacokinetics of nilotinib. The area under the serum concentration–time curve (AUC) and the maximum concentration in serum (C_{max}) was analyzed using analysis of variance (ANOVA). All statistical analyses were performed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA).

All patients provided written informed consent. The study protocol was approved by the Institutional Review Board of the Asan Medical Center.

Results

Patient characteristics

Seventeen patients with GIST entered the Compassionate Use Program at the Asan Medical Center during the study period (Table 1). Their median age at the start of nilotinib treatment was 59 years (range 35–71 years). The small intestine was the most common (53%) primary site, followed by the stomach (35%). The sum of uni-dimensional tumor measurements at baseline before nilotinib initiation was <20 cm in 9 patients (52.9%). At baseline, 12 patients (70.6%) had liver metastases and 9 (52.9%) had peritoneal metastases. All 17 patients had experienced disease progression on both imatinib and sunitinib. Fifteen patients (88.2%) had a history of at least one surgical intervention (small intestine resection, 9; liver resection, 8; major (subtotal or total) gastrectomy, 4; large intestine resection, 3). The median length of resected small intestine was 14.0 cm (range, 3.0–35.0 cm). Mutational analyses were available in 13 patients; *KIT* exon 11 mutations were the most common (69.2%), with 1 patient (7.7%) having a KIT exon 9 mutation and 1 (7.7%) having a PDGFRA exon 12 mutation.

Table 1 Clinical and Pathologic Characteristics of Patients at Initiation of Nilotinib Therapy

Characteristics	$N = 17$ (%)
Sex, *n* (%)	
Male	14 (82.4)
Female	3 (17.6)
Age (years), median (range)	59 (35–71)
Primary site, *n* (%)	
Stomach	6 (35.3)
Small intestine	9 (52.9)
Colorectum	1 (5.9)
Omentum	1 (5.9)
Sum of uni-dimensional tumor measurements, *n* (%)	
<20 cm	9 (52.9)
≥20 cm	8 (47.1)
Metastatic sites, *n* (%)	
Liver	12 (70.6)
Peritoneum	9 (52.9)
Time to progression on imatinib, *n* (%)[a]	
<24 months	7 (50.0)
≥24 months	7 (50.0)
Time to progression on sunitinib, *n* (%)	
<6 months	7 (41.2)
≥6 months	10 (58.8)
WHO performance status, *n* (%)	
0	2 (11.8)
1	14 (82.4)
2	1 (5.8)
Previous operation, *n* (%)	
Major gastrectomy[b]	4 (23.5)
Small intestine resection	9 (52.9)
Large intestine resection	3 (17.6)
Liver resection	8 (47.1)
Kinase mutation, *n* (%)[c]	
KIT exon 11	9 (69.2)
KIT exon 9	1 (7.7)
PDGFRA 12	1 (7.7)
Wild type	2 (15.4)

[a] Exact progression date was available for 14 patients

[b] Including subtotal and total gastrectomy

[c] Mutational analysis results were available for 13 patients

Pharmacokinetics

The serum concentration–time curves of the 17 patients taking 400 mg nilotinib twice daily showed large variability (Fig. 1a). The pharmacokinetic parameters, C_{max}, $T_{1/2}$ and $AUC_{0-12\ h}$, are summarized in Table 3. One patient had a prior gastric resection and small intestine resection; this patient was classified into the gastrectomy group. The mean serum concentration–time profiles of nilotinib according to previous resection of the stomach and small intestine are shown in Fig. 1b. The C_{max} and $AUC_{0-12\ h}$ were significantly lower in patients with a history of major gastrectomy than in patients with no previous gastric or small intestine resection (Table 2). ANOVA with log-transformed values of C_{max} and $AUC_{0-12\ h}$ revealed

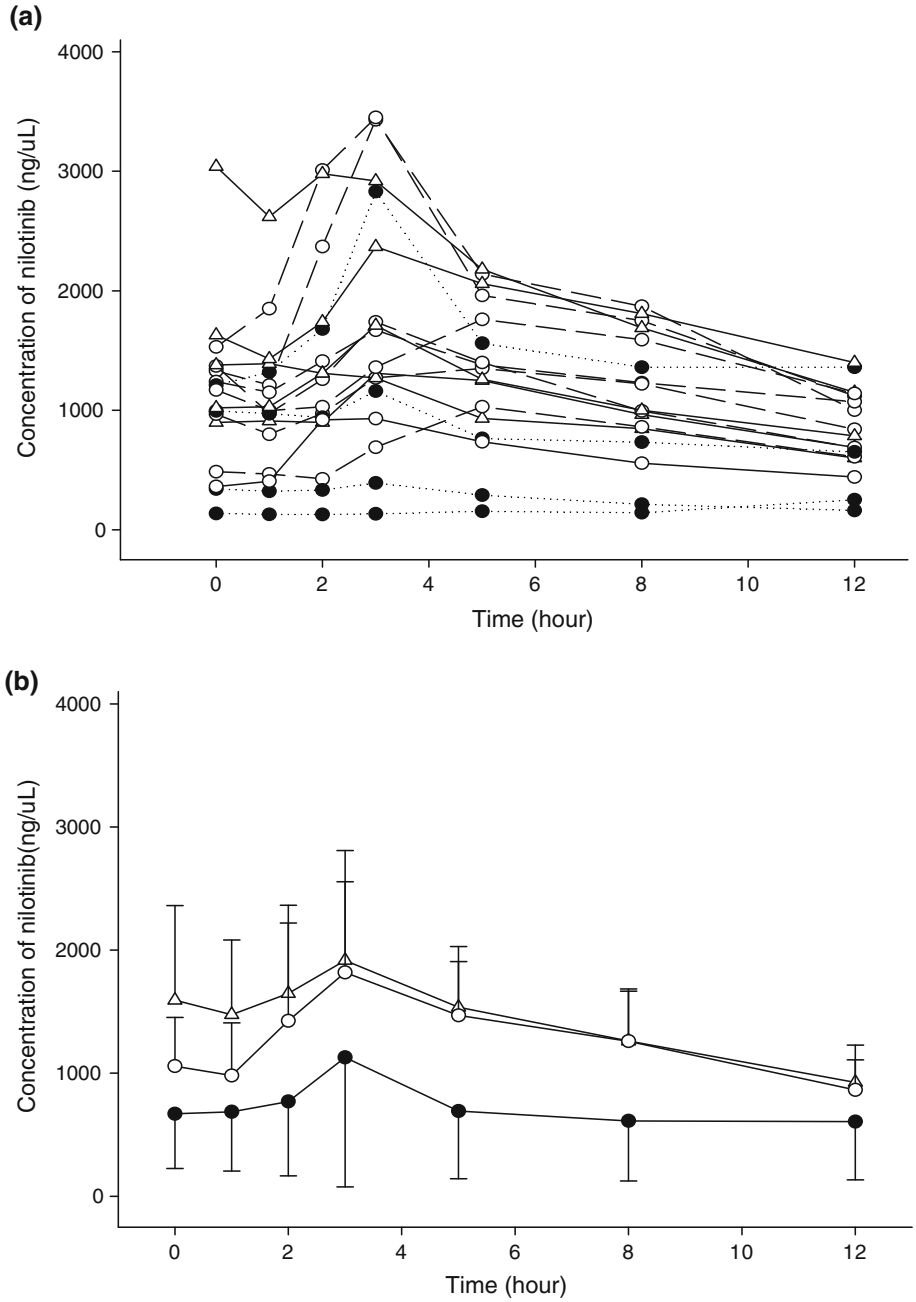

Fig. 1 Serum concentration–time profiles of nilotinib in patients with a prior history of gastrointestinal resection: gastrectomy (*filled circle*, $n = 4$), small intestine resection (*open circle*, $n = 8$) or neither (*open triangle*, $n = 5$), **a** Individual plots **b** Mean plots. On the individual plots, note the 2 gastrectomized patients with low concentrations of nilotinib

statistically significant differences between patients with and without previous major gastrectomy (Table 2; $P = 0.034$ and $P = 0.014$, respectively). Even among the four patients in the gastrectomized group, however, two patients showed lower values than the other two (Fig. 1a).

Tolerability

The median treatment duration was 37.1 weeks (range 4.3–69 weeks). At the analysis cut-off date, 13 patients (76.5%) had discontinued nilotinib treatment, all due to disease progression. No patient required dose reduction or discontinuation due to toxicities. Most adverse events were mild (grade 1, 41.2%; grade 2, 52.9%), with no grade 3/4 adverse events (Table 3). The tolerability profiles of patients with prior major gastrectomy, small intestine resection or neither were similar (data not shown).

Efficacy

All 17 patients have been evaluated for response and survival. Two patients showed partial response, and 10 (58.8%) had stable disease. The rate of clinical benefit at 24 weeks was 41.2% (Table 4). Median PFS was 23.6 weeks (95% CI 0–50.2 weeks), and median OS was 74.0 weeks (95% CI 8.7–139.3 weeks; Fig. 2). PFS and

Table 2 Nilotinib pharmacokinetic parameters in all GIST patients and in patients with and without prior gastric or small intestine resection (Mean ± SD)

	C_{max} (μg/L)	*P* value*	$AUC_{0-12\ h}$ (h μg/L)	*P* value*
Total ($n = 17$)	1,754 ± 969.8		14,190 ± 6,853	
Gastrectomy ($n = 4$, A)	1,158 ± 1,183		8,525 ± 7,869	
Small intestine resection ($n = 8$, B)	1,964 ± 732.2	A versus (B + C) 0.034	16,830 ± 6,141	A versus (B + C) 0.014
No prior resection of the stomach or small intestine ($n = 5$, C)	1,920 ± 988.2		15,370 ± 5,862	

* *P* values were calculated by comparing groups by ANOVA using log-transformed values of C_{max} and $AUC_{0-12\ h}$

Table 3 Summary of hematological and non-hematological toxicities

Adverse events	Toxicity grade, *n* (%) of patients		
	1	2	3/4
Abdominal pain	4 (23.4)	3 (17.6)	–
Nausea	2 (11.8)	–	–
Hyperbilirubinemia	–	2 (11.8)	–
Abdominal distension	–	1 (5.9)	–
Diarrhea	2 (11.8)	–	–
Constipation	1 (5.9)	–	–
Hemorrhoid	1 (5.9)	–	–
AST elevation	1 (5.9)	–	–
Facial rash	1 (5.9)	–	–
Systemic rash	2 (11.8)	3 (17.6)	–
Hand–foot skin reaction	1 (5.9)	–	–
Fatigue	4 (23.4)	–	–
Weight loss	–	3 (17.6)	–
Fever	–	1 (5.9)	–
Headache	1 (5.9)	2 (11.8)	–
Anorexia	4 (23.4)	–	–
Limb edema	–	2 (11.8)	–
Myalgia	5 (29.4)	–	–
Sensory neuropathy	1 (5.9)	–	–
Anemia	–	3 (17.6)	–
Hyperglycemia	1 (5.9)	–	–

OS did not differ significantly in patients with and without prior major gastrectomy and small intestinal resection (Table 4). Among the 4 gastrectomized patients, however, two (50%), with markedly decreased nilotinib exposure ($AUC_{0-12\ h}$ of 1,914 and 3,194 h μg/L), showed rapid disease progression (PFS of 4.6 and 7.1 weeks).

Discussion

We have investigated the pharmacokinetics, tolerability and efficacy of nilotinib (400 mg twice daily) in patients with imatinib- and sunitinib-resistant GIST, with prior major gastrectomy, small intestine resection or neither. Consistent with previous results, we found that nilotinib treatment could stabilize patients for several months and may therefore have a role as a third-line therapy in GIST [13, 19]. In addition, we assessed the relationships among prior gastrointestinal surgical interventions, nilotinib exposure and clinical outcome. Despite the small number of patients who were pharmacokinetically evaluated, major gastrectomy was associated with a significant decrease in the bioavailability of nilotinib and, at least in some patients, a reduction in clinical activity.

This study was performed within the Compassionate Use Program, and baseline characteristics of patients were similar to those of a retrospective European study of similar patients [13]. We found that 58.8% of our patients who developed resistance to imatinib and sunitinib achieved stable disease on nilotinib, with median PFS and OS of 6 and 18 months, respectively.

We observed a large interindividual variability in nilotinib pharmacokinetics, findings comparable to those of a previous phase 1 study in GIST patients from the US and Europe [19]. Nilotinib does not give rise to any major circulating metabolites and is primarily cleared by CYP3A4 metabolism. Nilotinib is also implied to be a substrate of P-gp [20]. CYP3A4 and P-gp polymorphisms may account for the interindividual variability.

Our pharmacokinetic analysis suggested that prior subtotal and total gastrectomy could decrease the bioavailability of nilotinib in some patients. We evaluated the comedications and diets of the two patients with especially low absorption; however, we could not identify factors that could account for the impaired absorption. On the other hand, gastrectomy can alter the absorption of nilotinib via various aspects. First, the solubility of nilotinib is pH dependent, and therefore may be affected by decreased gastric acid related to stomach resection. Esomeprazole, a proton pump inhibitor, has been reported to reduce the rate and extent of nilotinib absorption by 27 and 34%, respectively [21]. Nilotinib reaches its peak absorption concentrations following oral administration of 600 mg, without any significant increment at higher

Table 4 Rates of best overall response, clinical benefit at 24 weeks and progression-free survival in patients treated with nilotinib ($n = 17$)

	Best overall response				Clinical benefit rate at 24 weeks (%)	Progression-free survival (weeks)
	CR	PR	SD	PD		
Total	–	2	10	5	47.0	23.6 (0–50.6)
No resection ($n = 5$)	–	2	2	1	60.0	8.7, 23.6, 31.4[a], 47.1, 60.0[a]
Intestinal resection ($n = 8$)	–	–	6	2	50.0	3.9, 4.0, 14.0, 23.0, 25.3[a], 32.4[a], 47.7, 67.0[a]
Major gastrectomy ($n = 4$)	–	–	2	2[b]	25.0	4.6[b], 7.1[b], 23.4, 57.9

[a] Censored progression-free survival values

[b] Gastrectomized patients ($n = 2$) with low nilotinib exposure

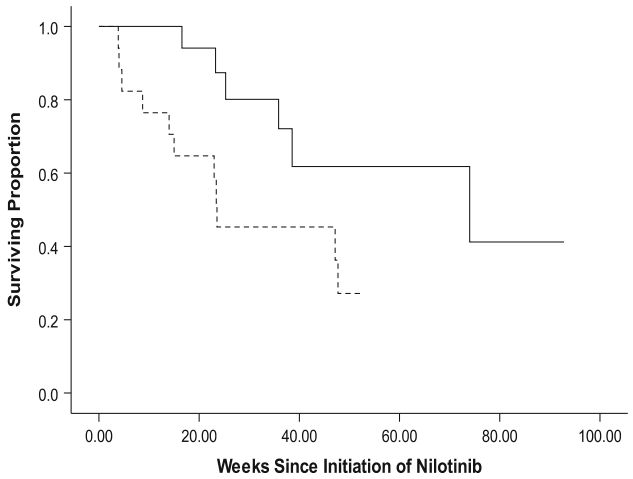

Fig. 2 Progression-free survival (*dotted line*) and overall survival (*solid line*) since initiation of nilotinib treatment

doses, a finding also suggesting its pH-dependent solubility-limited absorption [22]. Second, gastrectomy may have an effect on the gastrointestinal transit time of nilotinib. Food–nilotinib interaction studies show a pronounced increase in absorption when the drug is co-administered with a high-fat meal [14]. These increments may be related to the augmented in vivo dissolution of nilotinib and/or delayed gastric emptying, findings supported by observations of prolonged time to C_{max} with high-fat meals. Both decreased acid secretion and rapid gastric emptying may contribute by decreasing the absorption of imatinib, as suggested in a report on a patient who underwent gastric resection [23]. One patient in our study underwent both a major gastrectomy and small bowel resection and was included in the gastrectomy group. None of our gastrectomized patients reported specific symptoms of decreased gastric transit time, such as diarrhea or "dumping syndromes". As some gastrectomized patients did not show lower bioavailability of nilotinib, it is necessary to define the mechanism underlying the decreased bioavailability of this agent and identify patients who have difficulties absorbing this drug. Another possibility is that patients with rapid progression had different tumor biology. However, this was not supported by the data as there was no correlation between the progression-free survival (PFS) of nilotinib and time to progression (TTP) of imatinib and sunitinib, respectively.

Adequate blood concentrations are important for the efficacy of imatinib in patients with both CML and GIST, a principle that also applies to nilotinib in GIST patients [24, 25]. In our study, two of the four gastrectomized patients showed markedly lower absorption ($AUC_{0–12\ h}$ of 1,914 and 3,194 h μg/L) and rapid disease progression (PFS of 4.6 and 7.1 weeks). Although our findings are limited by the small sample sizes, they may have important clinical implications because patients with low exposure progressed within weeks of nilotinib initiation.

As many GIST patients undergo surgery on the gastrointestinal tract, monitoring serum concentrations of nilotinib may be important in clinical practice, especially in gastrectomized patients. This may be similar to the clinical situation in gastrectomized patients treated with imatinib [15]. Imatinib showed significantly lower trough levels at steady state in patients who underwent major gastrectomy. Furthermore, therapeutic drug monitoring may be potentially useful in patients treated with various TKIs [26]. Many of these agents are soluble in acidic milieu, but their solubility rapidly declines above pH 4. Thus, our results suggest that patients with prior gastrectomy should receive special attention regarding the absorption of these agents.

We have shown here that nilotinib is well tolerated and has clinical activity in GIST patients who have progressed on imatinib and sunitinib. Our pharmacokinetic results suggest that prior gastrectomy may lead to low bioavailability of nilotinib. Owing to the limited sample size, however, these pharmacokinetic conclusions should be interpreted with caution and further studies, in larger numbers of patients, are required to confirm the relationship between decreased exposure and lack of anticancer activity, that is, whether low absorption of nilotinib leads to decreased therapeutic efficacy.

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