A Phase I Study of Single-Agent Nilotinib or in Combination with Imatinib in Patients with Imatinib-Resistant Gastrointestinal Stromal Tumors

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Abstract

Purpose: To study the safety, tolerability, and pharmacokinetics of the selective tyrosine kinase inhibitor nilotinib as a single agent or in combination with imatinib in patients with advanced imatinib-resistant gastrointestinal stromal tumors.

Experimental Design: A phase I intercohort dose-escalation trial was done in patients who received either (a) single agent nilotinib 400 mg twice daily or (b) escalating doses of nilotinib (200 mg once daily, 400 mg qd, or 400 mg bid) plus imatinib 400 mg bid (10- and 14-hour interval daily), or (c) nilotinib 400 mg bid plus imatinib 400 mg qd. Safety, pharmacokinetics, and tumor assessments were done.

Results: Oral clearance (CL/F) of nilotinib was similar across the combination groups (mean CL/F, 19.1-25.6 L/h), and lower than in the single-agent cohort (mean CL/F, 35.6 L/h). A linear relationship between nilotinib daily dose and peak concentration was observed in the combination cohorts. Observed adverse events (AE) were mostly nonhematologic. Frequently reported AEs were rash (40%), fatigue (38%), abdominal pain (36%), and nausea (36%). Severe AEs (grade 3 or 4) included abdominal pain (13%) and rash (9%), the latter mainly with the combination. Thirty-eight patients had stable disease and two patients achieved partial response with a median progression-free survival of 134 days for the entire group.

Conclusions: Nilotinib alone or in combination with imatinib was well tolerated overall and showed clinical activity in imatinib-resistant gastrointestinal stromal tumor patients. This phase I trial identified single-agent nilotinib 400 mg bid or combined with imatinib 400 mg qd as possible phase II doses for further evaluation. (Clin Cancer Res 2009;15(18):5910-6)

Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors of the gastrointestinal tract (1). The majority of GISTs (90%) harbor activating mutations in the KIT or platelet-derived growth factor receptor α (PDGFRA) receptor tyrosine kinases. The characteristic pathogenic feature of any GIST is the presence of aberrantly activated signaling through either KIT or PDGFRA receptor tyrosine kinases (2, 3).

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Translational Relevance

Although imatinib has been shown to be successful in the treatment of surgically incurable gastrointestinal stromal tumor, some patients develop resistance to imatinib. Sunitinib, another receptor tyrosine kinase inhibitor, has been used to treat imatinib-resistant patients, but the short benefit and strong adverse effects make it a less desirable drug. This phase I trial in patients with imatinib-resistant gastrointestinal stromal tumor showed that nilotinib alone or in combination with imatinib could provide an alternative to imatinib-resistant patients, and possibly prevent or overcome imatinib resistance. This initial study explored the use of nilotinib as third-line treatment, and identified possible doses for further phase II evaluations.

Imatinib is a highly effective therapy for surgically incurable GIST, with >80% tumor control rates and median survival close to 5 years (4–6). However, a subset of patients (estimated between 5% and 14%) may exhibit primary resistance to imatinib within the first 6 months of therapy, especially patients with wild-type KIT tumors or KIT exon 9 mutations (5). Secondary resistance evolves in most patients after a median of 2 years of therapy (7, 8). Sunitinib, the only second-line tyrosine kinase inhibitor (TKI) currently available for GIST, has shown significant clinical benefit in patients whose disease has progressed during, or who are intolerant to imatinib therapy (9). Unfortunately, the benefit of such second-line therapy is even shorter (~9 months), and a relatively high incidence of serious adverse events (AE) including hypothyroidism and cardiotoxicity has been reported (10, 11).

Many studies have shown that treatment of GIST with TKIs, such as imatinib and sunitinib, eventually results in the development of tumor clones, which are resistant to these agents (8, 12–16). These observations suggest that no single kinase inhibitor will effectively inhibit all mutant clones, and provide the rationale for developing alternative agents so that effective broad-spectrum, noncross-resistant combination therapies will eventually be feasible.

Nilotinib (Tasigna, formerly known as AMN107; Novartis) is a rationally designed second-generation selective TKI, which potently inhibits BCR-ABL, KIT, and PDGFRs and has shown clinical activity in chronic myeloid leukemia (CML; refs. 17, 18). Nilotinib and imatinib exhibit similar in vitro potency against KIT and PDGFR kinases (19). However, they differ in their mechanism of cellular transport, resulting in 5- to 10-fold higher intracellular levels of nilotinib than imatinib (20, 21). Furthermore, nilotinib has shown in vitro antiproliferative activity at physiologically relevant concentrations in imatinib-resistant human GIST cell lines, as well as in TKI-resistant GIST patients (22, 23). Due to the polyclonal nature of GIST, evidence suggests that part of a tumor might still be under partial imatinib control at progression, suggesting that combining AMN107 with imatinib may have a synergistic effect in GIST.

This phase I trial was designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of nilotinib in patients with imatinib-resistant GIST, either as a single agent or in combination with imatinib. The rationale for testing the combination of nilotinib with imatinib in GIST patients was based on two major justifications: first, in vitro data from CML cell lines, suggesting that this combination might have synergistic cytotoxic activity (24, 25), and second, there is a strong mechanistic structural biology argument in favor of simultaneously targeting multiple different mutationally activated molecular variants of the KIT and PDGFRA kinases in GIST.

Patients and Methods

Patients. Patients ages ≥18 y with histologically confirmed unresectable and/or metastatic GIST, who had shown objective disease progression using Response Evaluation Criteria in Solid Tumors (26) during previous imatinib therapy at a dose of at least 800 mg daily were eligible. Up to six GIST patients intolerant to imatinib 800 mg daily were also allowed in the study. Previous therapy with other TKIs was permitted, provided patients had fully recovered from any toxicity attributed to these agents. Previous chemotherapy was also allowed, provided it had been discontinued ≥24 wk earlier. A WHO performance status of 0 or 1 was required. Patients had normal electrolytes and adequate bone marrow, hepatic, and kidney function (absolute neutrophil count ≥1,500/μL; platelets of ≥100,000/μL; potassium, calcium, magnesium, or phosphorus is greater than or equal to lower limit of normal; alanine aminotransferase (ALT) and aspartate aminotransferase (AST), or alkaline phosphatase ≤2.5× upper limit of normal (ULN); serum bilirubin, amylase, and lipase, or creatinine ≤1.5× ULN. Major exclusion criteria included abnormal cardiac function left ventricular ejection fraction, <45%; right and left bundle branch block; pacemaker use; ST depression, >1 mm; congenital QT syndrome; ventricular or atrial tachyarrhythmias; bradycardia (<50 beats per minute); QTC >450 ms on screening electrocardiogram; myocardial infarction 12 mo before starting AMN107; unstable angina during the past 12 mo; significant heart disease and prior or concomitant malignancies other than GIST. All patients provided written informed consent. The institutional review boards at all participating sites approved the study protocol.

Study design. In this open-label, phase I, dose-escalation study, patients were assigned sequentially either to: (a) single-agent nilotinib 400 mg bid (the dose currently recommended for hematologic malignancies; ref. 18); or (b) interchohort escalating doses of nilotinib (200 mg qd, 400 mg qd, or 400 mg bid) in combination with imatinib 400 mg bid (10- and 14-h interval daily); or (c) nilotinib 400 mg bid plus imatinib 400 mg qd. Nilotinib and imatinib were each administered by continuous daily oral dosing. Morning doses were taken with a light breakfast; nightly doses of imatinib were taken with dinner, whereas nilotinib was taken 2 h after imatinib. Study drug administration was discontinued with disease progression, unacceptable toxicity, or withdrawal of consent. Assignment to treatment was based on Bayesian inference of a logistic model describing the dose-toxicity relationship and was guided by the escalation with overdose control principle (see Statistical Methods section; ref. 27). Once the dose-escalation part of the study was completed and maximum tolerated dose determined, further safety, PK, and tumor response data were collected by expanding the cohort at the recommended phase II dose level.

Dose escalation was stopped when patients experienced dose-limiting toxicity (DLT), defined as grade 4 neutropenia absolute neutrophil count of <500/mm³ lasting ≥7 d; grade 3 or 4 febrile neutropenia absolute neutrophil count of <1,000/mm³ with fever of >101°F; grade 4 thrombocytopenia, platelet counts of <50,000/mm³ lasting ≥7 d; serum creatinine of ≥2.0 to ≤3.0× ULN lasting ≥7 d; serum creatinine of >3.0× ULN; total bilirubin of ≥2 to ≤3.0× ULN lasting ≥7 d; total bilirubin of >3.0× ULN (unless the hyperbilirubinemia was due to an indirect component only); grade 3 or 4 AST/ALT for ≥7 d; grade ≥2 pancreatitis; any clinically significant grade ≥2 serious AEs related to study treatment causing ≥7 d of interruption of drug therapy; skin toxicity sufficiently severe to require dose reduction; nausea and vomiting if severe (≥grade 1) and refractory to antiemetics; or diarrhea if severe (≥grade 1) and refractory to antidiarrheal therapies.
Study assessments. Safety was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (28). Following baseline evaluations, physical examination, WHO performance status assessment, hematology (hemoglobin, hematocrit, platelets, total WBC count, and differential) and serum biochemistry (sodium, calcium, potassium, chloride, magnesium, phosphorus, bicarbonate, creatinine, glucose, urea, uric acid, albumin, total protein, AST, ALT, total bilirubin, alkaline phosphatase, lipase, amylase, triglycerides, and cholesterol) were done every 2 wk during the first 2 mo of treatment and every month thereafter. Cardiac safety was monitored during the study by serial electrocardiograms on day 1 and 8, then monthly thereafter or if clinically indicated. Tumor assessments included computed tomography scan or magnetic resonance imaging at baseline, after 1 and 2 mo on study and then every 2 mo thereafter. Tumor responses were analyzed according to Response Evaluation Criteria in Solid Tumor (26). Available baseline, pretreatment GIST biopsies were analyzed for KIT and PDGFRA genotype.

Pharmacokinetics. Blood sampling for determination of the serum concentrations of nilotinib at steady-state was done on day 8 or day 15 as follows: 0 (predose), 1, 2, 3, 5, 10, and 24 h postdose for the daily regimens and predose, 1, 2, 3, 5, 10, 12, and 24 h postdose for the bid regimens. Blood sampling for determination of plasma concentrations of imatinib and des-methyl-imatinib metabolite were done on day -1 (imatinib alone) and day 8 or day 15 (imatinib in combination with nilotinib) as follows: 0 (predose), 1, 2, 3, 5, 10, and 24 h postdose. Drug concentrations were determined using the validated assay methods of liquid chromatography-tandem mass spectrometry (29). The lower limit of quantification was 10 ng/mL for both compounds and metabolite.

Statistical methodology. A five-parameter logistic model was used to describe the safety profile for single-agent nilotinib or in combination with three doses of imatinib (400, 600, or 800 mg). Historical data for single-agent nilotinib and imatinib DLT rates were used to set up the model. The primary objective of this design was to find the dose maximizing the probability that the true DLT rate lie in the 20% to 35% interval. Upon completion of 28 d, dosing and safety observation for each cohort estimates of the five parameters were updated and the dose-toxicity relationship for single-agent and combination therapy was derived. New cohorts ranged in size from three to six patients, whereas some combinations below the new level were expanded with additional patients. Any imatinib intolerant patients went into the nilotinib 400 mg bid and any additional imatinib-resistant patients went into the previously tested combination. Using data from all patients completing cycle 1 or experiencing DLT during cycle 1 at the completion of the first course of treatment, the Bayesian inference (30, 31) on the model parameters allowed quantification of the estimated risk of a dose or combination being unacceptably toxic, i.e., risk of the true rate of DLT for any dose or combination being >35%. A limit on this risk was set to 25% and any dose estimated to exceed this risk was excluded. This conservative escalation approach to find the maximum tolerated dose defined above allowed investigators to select the next dose or combination from a predicted set of acceptable doses. Other clinical data, e.g., drug-specific DLTs, PK information, or emerging efficacy data, could be used to determine appropriate doses of nilotinib and imatinib (30, 31).

The following PK parameters were estimated using standard non-compartmental methods: peak concentration (C\text{max}) time to reach \(t\text{max}\); area under the concentration-time curve from time zero to \(t\text{last}\) in a dosing interval (AUC\text{0-last}); \(t\text{last}\) is the time of the last available quantifiable drug concentration in a dosing interval; area under the concentration-time curve from time zero to the end of a dosing interval (AUC\text{0-\infty}); oral clearance at steady-state (CL/F), and average serum drug concentration in a dosing interval (\(C\text{avg}\)) estimated by dividing AUC\text{0-\infty} by \(t\text{last}\). Descriptive statistics of PK parameters included mean, SD, and range. Median values with ranges are presented for \(t\text{max}\).

Kaplan-Meier estimates were computed for progression-free survival (PFS).

Results

Patients. A total of 53 patients were enrolled in the study from August 2005 to July 2006, at five participating centers (two in the United States and one each in France, Germany, and Italy). Data are presented as of November 2006. Fourteen patients were still on study at the data cutoff date.

Twenty-one (40%) patients had a primary cancer site in the small intestine and the majority of tumors (n = 48; 91%) were imatinib resistant (Table 1). Most patients (n = 42; 79%) had previously received imatinib for ≥24 months. Approximately 60% of patients experienced disease progression after 1 year of imatinib therapy and 20% during the first 6 months. The majority of patients had experienced disease progression on additional TKI therapies, most commonly sunitinib (n = 33; 62%).

The median dose intensity of nilotinib and imatinib corresponded to 98% to 100% of the planned daily dose for the single-agent cohort and all combination cohorts, except for the nilotinib 800 mg plus imatinib 800 mg cohort where it was ~60%.

The median duration of treatment was 134 days across all cohorts (range, 8-430 days). Thirty-nine patients (74%) discontinued the study. The most common primary reason for discontinuation was disease progression (n = 32; 60%), followed by AE (n = 3; 6%) and death (n = 2; 4%).

Tolerability and dose-limiting toxicities. Dose-limiting toxicities were rash and elevated bilirubin. Rash was the DLT in 5 patients receiving combination therapy, occurring in 2 of 5 (40%) patients receiving nilotinib 400 mg bid and imatinib 400 mg bid, and 3 of 16 (19%) patients receiving nilotinib 400 mg bid and imatinib 400 mg daily. The high frequency of severe skin rash in patients receiving nilotinib 400 mg bid and imatinib 400 mg bid resulted in dose reduction in all five patients, and no further dose escalation was undertaken. One of 18 (6%) patients in the single-agent nilotinib 400 mg bid.

Table 1. Patient demographics and baseline disease characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 53 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>31 (59)</td>
</tr>
<tr>
<td>WHO performance status, n (%)</td>
<td>29 (55)</td>
</tr>
<tr>
<td>Grade 0</td>
<td>23 (43)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Primary site of cancer, n (%)</td>
<td>3 (6)</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
</tr>
<tr>
<td></td>
<td>Other*</td>
</tr>
<tr>
<td>Time on imatinib, n (%)</td>
<td>&lt;6 mo</td>
</tr>
<tr>
<td></td>
<td>≥6 to &lt;12 mo</td>
</tr>
<tr>
<td></td>
<td>≥12 to &lt;24 mo</td>
</tr>
<tr>
<td></td>
<td>≥24 mo</td>
</tr>
<tr>
<td>Other prior TKI treatment, n (%)</td>
<td>AMG706, RADD001, dasatinib, or VEG10003</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>12 (23)</td>
</tr>
</tbody>
</table>

Abbreviations: DSD, standard deviation; WHO, world health organization
*Includes colon, peritoneum, rectum, and other abdominal sites.
Neutropenia was reported as a laboratory abnormality in one AE. There were no episodes of thrombocytopenia.

cohort, with grade 2 elevated bilirubin at study entry, experienced grade 3 dose-limiting hyperbilirubinemia and was discontinued from the study.

The frequency of DLT in the nilotinib 400 mg bid plus imatinib 400 mg qd cohort (19%) was considered acceptable (i.e., the Bayesian model predicted only a 3% chance for this combination of being excessively toxic and a 47% chance of having an acceptable safety profile). Therefore, the combination dose of nilotinib 400 mg bid and imatinib 400 mg qd was deemed appropriate for future phase II combination studies, as was the single-agent nilotinib 400 mg bid dose.

Safety. All patients experienced AEs during the study with the most frequently reported AEs being nonhematologic AEs grade 1 or 2 (Table 2). The safety profiles of single-agent nilotinib or in combination with imatinib were generally similar. Overall, the most frequent AEs were rash (40%), fatigue (38%), abdominal pain (36%), and nausea (36%). Rash was more common in the combination cohorts and was generally manageable with temporary dose interruptions and/or topical corticosteroids. Fatigue and abdominal pain were more frequent in the single-agent nilotinib cohort. Peripheral edema was uncommon and reported only in the combination cohorts. Grade 3 or 4 toxicities occurred in 49% of patients overall (Table 2) and resulted in discontinuation from the study in two patients: hyperbilirubinemia in one patient treated with nilotinib 400 mg bid single-agent and rash in the other receiving nilotinib 400 mg bid plus imatinib 400 mg bid.

Hematologic toxicities were uncommon with only anemia reported as AE. There were no episodes of thrombocytopenia. Neutropenia was reported as a laboratory abnormality in one patient treated with nilotinib 200 mg plus imatinib 400 mg bid, without neutropenic fever.

The most frequent grade 3 or 4 laboratory abnormalities were hypophosphatemia (12%), which was more common in the combination cohorts, and hyperbilirubinemia (8%), which was more frequent in the single-agent nilotinib cohort. Grade 3 elevations of AST or ALT were uncommon (<2% overall), did not result in drug discontinuation and were reversible upon dose interruption.

One patient with a history of episodes of junctional rhythm and supraventricular arrhythmias developed atrial fibrillation that was considered related to nilotinib; nilotinib was continued without dose reduction or interruption. Four patients (13%) exhibited clinically insignificant postbaseline QTcF interval of >500 ms, one patient in the nilotinib 400 mg bid plus imatinib 400 mg bid cohort, and three patients in the nilotinib 400 mg bid plus imatinib 400 mg daily combination. None of these four patients experienced cardiac events during the study and no QTcF of >500 ms was reported.

Antitumor activity and clinical outcomes. Overall, two Response Evaluation Criteria in Solid Tumor–defined partial responses were observed, one in a patient who had progressed during adjuvant imatinib and was intolerant to imatinib 800 mg, the other in a patient who had failed multiple regimens including imatinib and sunitinib (Table 3). The median duration of response was 197 days. The majority of patients (78%) had stable disease. Thirteen patients (72%) in the single-agent nilotinib cohort had stable disease lasting for >4 months in 9 (50%) patients and >6 months in 5 (28%) patients. Of the 16 patients treated with the combination cohort selected for further phase II studies...
(nilotinib 400 mg bid and imatinib 400 mg qd), 9 had stable disease. The median PFS for the patients in the nilotinib single-agent group was 168 days (range, 1-393 days) and among all patients was 134 days (range, 1-393 days). The median PFS was not reached for the patients in both the nilotinib 400 mg bid plus imatinib 400 mg bid and the selected phase II dose cohorts (Table 3). The Kaplan-Meier estimate of PFS at 6 months was 56% for the phase II combination cohort compared with 47% for the single-agent group (Table 3).

**KIT** mutations were found in 19 of 23 (83%) patients; none of the analyzed tumors had **PDGFR** mutations (data not shown).

**Pharmacokinetics.** Nilotinib dose proportionality was observed during combination treatments. There was a linear relationship between \(C_{\text{max}}\) or \(C_{\text{avg}}\) and total nilotinib daily dose for the combination cohorts (slope, 0.881 and 0.946, respectively, based on power model). \(CL/F\) of nilotinib was similar across the four combination groups, but lower than that in the single-agent cohort. In comparison with the single-agent cohort, the AUC\(_{0-t}\) values of nilotinib were 40% and 18% higher in the nilotinib 400 mg bid combination cohorts (Table 4).

As compared with monotherapy (day -1), the AUC\(_{0-t}\) values of imatinib were found to be increased by 18% to 39% during the combination therapy with nilotinib 200 mg qd, 400 mg qd, or 400 mg bid doses (Table 5).

**Discussion**

The current study represents the first trial to examine single-agent nilotinib and in combination with imatinib in patients with imatinib-resistant GIST. In this resistant patient population, nilotinib alone or in combination with imatinib was generally well tolerated. We administered nilotinib and imatinib at doses similar to the single-agent standard doses with an acceptable safety profile: nilotinib 400 mg bid with or without the combination of imatinib 400 mg bid were the recommended doses for further clinical development. The Bayesian model provided a flexible dose escalation scheme where clinical experience could be combined with information on DLT probabilities leading to a more informed decision making on study.

Overall, toxicities noted in association with nilotinib-based treatments were mild to moderate, mostly nonhematologic and consistent with the previous experience in CML (18). Most grade 3 or 4 toxicities were considered unrelated to study medication, and

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**Table 3. Best overall response**

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Nilotinib 400 mg bid n = 18</th>
<th>Nilotinib 200 mg qd/imatinib 400 mg bid n = 7</th>
<th>Nilotinib 400 mg bid/imatinib 400 mg bid n = 7</th>
<th>Nilotinib 400 mg bid/imatinib 400 mg bid n = 5</th>
<th>Nilotinib 400 mg bid/imatinib 400 mg qd n = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>1 (6)</td>
<td>0</td>
<td>1 (14)</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13 (72)</td>
<td>7 (100)</td>
<td>5 (71)</td>
<td>4 (80)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (11)</td>
<td>0</td>
<td>1 (14)</td>
<td>0</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Unknown*</td>
<td>1 (6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N/A†</td>
<td>1 (6)</td>
<td>0</td>
<td>1 (14)</td>
<td>1 (20)</td>
<td>0</td>
</tr>
</tbody>
</table>

PFS—Kaplan-Meier estimates

| Rate at 4 mo, % | 59                           | 83                                        | 43                                        | 50                                        | 56                                        |
| Rate at 6 mo, % | 47                           | 17                                        | 29                                        | 50                                        | 56                                        |
| Median, d       | 168                          | 143                                       | 112                                       | Ongoing                                   | Ongoing                                   |
| Range           | 1-393                       | 143                                       | 112                                       | Ongoing                                   | Ongoing                                   |
| Median follow-up, d | 186                       | 153                                       | 113                                       | 167                                       | 126                                       |

*Best response could not be classified as partial or complete response, progressive, or stable disease.
†Not assessed: patients had discontinued study before the first postbaseline tumor assessment.

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**Table 4. Summary statistics of Nilotinib pharmacokinetic parameter values at steady-state (day 8 or 15)**

<table>
<thead>
<tr>
<th>Nilotinib dose</th>
<th>Cohort 1 n = 15</th>
<th>Cohort 2 n = 6</th>
<th>Cohort 3 n = 6</th>
<th>Cohort 4 n = 5</th>
<th>Cohort 5 n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib dose</td>
<td>400 mg bid</td>
<td>200 mg qd</td>
<td>400 mg qd</td>
<td>400 mg bid</td>
<td>400 mg bid</td>
</tr>
<tr>
<td>Imatinib dose</td>
<td>0 mg</td>
<td>0 mg</td>
<td>400 mg bid</td>
<td>400 mg bid</td>
<td>400 mg bid</td>
</tr>
<tr>
<td>(t_{\text{max}}), h</td>
<td>2.8 (0-9.9)</td>
<td>4.0 (2.9-6.3)</td>
<td>6.4 (1.9-23.8)</td>
<td>2.1 (0-12.5)</td>
<td>0 (0-5.0)</td>
</tr>
<tr>
<td>(C_{\text{max}}), ng/mL</td>
<td>1,644 ± 828</td>
<td>655 ± 277</td>
<td>1,236 ± 705</td>
<td>2,160 ± 756</td>
<td>2,509 ± 1,266</td>
</tr>
<tr>
<td>(C_{\text{avg}}), ng/mL</td>
<td>1,172 ± 587</td>
<td>438 ± 150</td>
<td>863 ± 472</td>
<td>1,617 ± 610</td>
<td>1,642 ± 701</td>
</tr>
<tr>
<td>AUC(_{0-t}), ng\cdot h/mL</td>
<td>13,636 ± 6,617</td>
<td>10,474 ± 3,491</td>
<td>20,498 ± 11,135</td>
<td>18,717 ± 8,516</td>
<td>16,760 ± 9,450</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>35.6 ± 16.7*</td>
<td>21.5 ± 9.3*</td>
<td>25.6 ± 13.8*</td>
<td>24.8 ± 10.0*</td>
<td>19.1 ± 6.1†</td>
</tr>
</tbody>
</table>

NOTE: Median (range) for \(t_{\text{max}}\), and mean ± SD for other PK parameters.
*CL/F was estimated as dose/AUC\(_{0-t}\).
†\(n = 3\); CL/F was estimated as dose/AUC\(_{t}\).
included abdominal pain, nausea, vomiting and increased bilirubin, AEs expected in patients with advanced GIST.

Skin toxicity is a common side effect of treatment with imatinib or nilotinib in advanced GIST and CML, and skin rash in this study was particularly severe in the combination groups (4, 18). This might be due to a potential biological effect of nilotinib and imatinib, as only a slight pharmacokinetic interaction was observed between these two drugs in this study.

The lower CL/F in all four combination cohorts compared with the single-agent group suggests that imatinib might have inhibitory effects on the clearance of nilotinib. This effect seemed to be dose-independent as the CL/F values of nilotinib were similar in the total daily dose range of 200 to 800 mg, when administered concurrently with either imatinib 400 mg qd or 400 mg bid. In single-agent nilotinib 400 mg bid cohort, the mean C_{max} and AUC values of nilotinib were comparable with values reported previously in the CML patients following nilotinib doses of 400 mg bid for 8 days (18). These results indicate that the pharmacokinetic profiles of nilotinib in this group of patients with GIST seemed to be similar to those in CML patients.

Nilotinib seemed to show clinical activity in refractory GIST, both as single-agent and in combination with imatinib. The majority of patients achieved stable disease for some period of time. Interpretation of the tumor responses and relationship to KIT mutational status is limited by the small sample size in each cohort. However, further investigation of the effect of nilotinib single-agent or in combination with imatinib in patients with advanced GIST with different KIT or PDGFRA mutations is warranted.

Our data show that nilotinib, either as a single agent or in combination with imatinib, was overall reasonably well tolerated and shows clinical activity in some patients with imatinib-resistant GIST. Nilotinib alone or in combination with imatinib could provide an alternative strategy for preventing or overcoming imatinib resistance in patients with GIST. A phase III study of nilotinib versus best supportive care with or without TKIs in patients with GIST who have progressed during prior therapy with imatinib and sunitinib has been completely accrued and the results are pending.

Acknowledgments

We thank the patients who participated in this study, as well as the collaboration and commitment of all investigators and their staff, without whom the study would not have been possible.

References


Table 5. Summary statistics of Imatinib pharmacokinetic parameter values of imatinib administered as 400 mg bid (day -1) and during combination therapy with nilotinib (day 8 or 15).

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Nilotinib dose</th>
<th>Study day</th>
<th>t_{max} h</th>
<th>C_{max} ng/mL</th>
<th>C_{avg} ng/mL</th>
<th>AUC_{0-t} ng*h/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 2 (n = 6)</td>
<td>200 mg qd</td>
<td>Day -1</td>
<td>2.5 (1.8-9.8)</td>
<td>2,768 ± 1,142</td>
<td>2,381 ± 1,181</td>
<td>18,070 ± 5,686</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 8</td>
<td>2.9 (1.9-5.5)</td>
<td>3,370 ± 1,117</td>
<td>2,768 ± 1,039</td>
<td>24,463 ± 4,884</td>
</tr>
<tr>
<td>Cohort 3 (n = 7)</td>
<td>400 mg qd</td>
<td>Day -1</td>
<td>4.8 (2.0-5.0)</td>
<td>4,020 ± 2,173</td>
<td>3,594 ± 2,195</td>
<td>33,445 ± 23,883</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 8</td>
<td>2.4 (0.9-5.0)</td>
<td>4,203 ± 1,121</td>
<td>3,735 ± 1,212</td>
<td>34,593 ± 13,319</td>
</tr>
<tr>
<td>Cohort 4 (n = 5)</td>
<td>400 mg bid</td>
<td>Day -1</td>
<td>3.0 (9.8-9.8)</td>
<td>4,170 ± 1,757</td>
<td>3,556 ± 1,523</td>
<td>31,703 ± 14,614</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 8</td>
<td>2.5 (2.0-3.1)</td>
<td>5,074 ± 2,758</td>
<td>4,285 ± 2,325</td>
<td>42,440 ± 24,349</td>
</tr>
</tbody>
</table>

NOTE: Median (range) for t_{max} and mean ± SD for other PK parameters.

Disclosure of Potential Conflicts of Interest

S. Bailey is employed by Novartis; P. Reichardt has received honoraria from the Novartis speakers’ bureau; W. Cheung has an ownership interest with Novartis; P. Cassier and M. von Mehren have received commercial research grants from Novartis; J. Blay, D. Pink, I. Ray-Coquard, M. Debic-Rychter, P. Casali, and A. Reichardt have received honoraria from the Novartis speakers’ bureau; J. Blay, M. Debic-Rychter, P. Reichardt, M. von Mehren, and P. Casali are consultants with Novartis; P. Casali is a consultant with Medimmune; R. Bertulli and E. Fumagalli provided expert testimony for Novartis; E. Fumagalli has received travel reimbursement from Novartis; G. Demetri is a consultant for Kolltan, Novartis, Pfizer, Ariad, Johnson & Johnson, Genentech, Infinity Pharmaceuticals, Aihyam, Idera, Bayer/EMD-Serono, Amgen, PamlGenex, and Flexikon and has received honoraria from Novartis and Pfizer.

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A Phase I Study of Single-Agent Nilotinib or in Combination with Imatinib in Patients with Imatinib-Resistant Gastrointestinal Stromal Tumors

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