

ORIGINAL ARTICLE

Nilotinib in Imatinib-Resistant CML and Philadelphia Chromosome–Positive ALL

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ABSTRACT

BACKGROUND

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Resistance to imatinib mesylate can occur in chronic myelogenous leukemia (CML). Preclinical in vitro studies have shown that nilotinib (AMN107), a new BCR-ABL tyrosine kinase inhibitor, is more potent than imatinib against CML cells by a factor of 20 to 50.

METHODS

In a phase 1 dose-escalation study, we assigned 119 patients with imatinib-resistant CML or acute lymphoblastic leukemia (ALL) to receive nilotinib orally at doses of 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, 800 mg, and 1200 mg once daily and at 400 mg and 600 mg twice daily.

RESULTS

Common adverse events were myelosuppression, transient indirect hyperbilirubinemia, and rashes. Of 33 patients with the blastic phase of disease, 13 had a hematologic response and 9 had a cytogenetic response; of 46 patients with the accelerated phase, 33 had a hematologic response and 22 had a cytogenetic response; 11 of 12 patients with the chronic phase had a complete hematologic remission.

CONCLUSIONS

Nilotinib has a relatively favorable safety profile and is active in imatinib-resistant CML. (ClinicalTrials.gov number, NCT00109707.)

THE CHIMERIC *BCR-ABL* GENE, CREATED BY the formation of the Philadelphia chromosome (Ph), encodes a fusion protein, BCR-ABL. The unregulated activity of the ABL tyrosine kinase in BCR-ABL is the cause of chronic myeloid leukemia (CML). Imatinib mesylate, an inhibitor of the BCR-ABL tyrosine kinase, improves the outcome in CML.^{1,2} However, the annual progression rate during treatment of chronic-phase CML with imatinib is 4 percent.³ Imatinib is active alone or in combination in newly diagnosed Ph-positive acute lymphoblastic leukemia (ALL).⁴⁻⁷

Nilotinib (AMN107, Novartis) is a new, orally active, aminopyrimidine-derivative tyrosine kinase inhibitor that is more potent against CML cells in vitro than is imatinib.⁸⁻¹² Like imatinib, nilotinib functions through competitive inhibition at the ATP-binding site of BCR-ABL, leading to the inhibition of tyrosine phosphorylation of proteins that are involved in the intracellular signal transduction that *BCR-ABL* mediates. Nilotinib has a higher binding affinity and selectivity for the ABL kinase than does imatinib. It also has 20 to 50 times the inhibitory activity of imatinib in imatinib-sensitive CML cell lines and 3 to 7 times the activity in imatinib-resistant cell lines. Nilotinib was also active in 32 of 33 imatinib-resistant cell lines with mutant ABL kinases.⁸⁻¹² This report summarizes the results of a phase 1 dose-escalation study of nilotinib in patients with CML and Ph-positive ALL whose disease was resistant to imatinib.

METHODS

PATIENTS

Patients with Ph-positive imatinib-resistant CML or ALL were eligible. Accelerated and blastic phases of CML were defined as previously described.¹³⁻¹⁶ Patients with a platelet count of 800,000 per cubic millimeter or more or with clonal evolution were also considered to have the accelerated phase of disease. Clonal evolution was defined by the presence of additional chromosomal abnormalities in the Ph-positive cells, excluding variant Ph translocations, a loss of chromosome Y, or constitutional abnormalities.^{13,14} Patients with only clonal evolution have a better prognosis and were analyzed separately.¹⁷ Patients with imatinib-resistant chronic-phase CML were enrolled in the study after the first four dose cohorts. Imatinib resistance was defined as a lack of complete hematologic response after 3 months of imatinib treatment, a lack of any

cytogenetic response (Ph-positive cells, >95 percent) after 6 months of treatment, a lack of a substantial cytogenetic response (Ph-positive cells, >35 percent) after 12 months of treatment, or a relapse after a hematologic response or a substantial cytogenetic response.

Patients had to be at least 18 years of age and have an adequate performance status and normal hepatic, renal, and cardiac function. Patients who had received imatinib therapy seven days before or hydroxyurea two days before the study began were not eligible to participate. The study was conducted in accordance with the Declaration of Helsinki. Patients gave written informed consent, according to institutional guidelines. The study was approved by the institutional review board at each study center.

STUDY DESIGN AND THERAPY

The study was designed to evaluate the safety and tolerability of nilotinib. Patients were successively assigned to one of nine dose cohorts, ranging from 50 to 1200 mg once daily and from 400 to 600 mg twice daily. Patients received nilotinib daily unless unacceptable adverse events or disease progression occurred. Dose escalation (not exceeding two dose levels beyond the level administered to newly enrolled patients) was permitted for patients with an inadequate response and no prohibitive toxic effects. Patients who had been treated at lower doses had the option to receive higher doses, with escalation to a level that was declared safe. During the first cycle of therapy or at times of worsening disease before inpatient dose escalation, patients were allowed to receive cytoreductive therapy (leukaphereses and hydroxyurea) to control elevated counts of blasts, platelets, or both. Responses in patients requiring leukapheresis or hydroxyurea concurrently with nilotinib could not be evaluated. The selection of the dose and the determination of the maximum dose that was tolerated followed a continuous modified reassessment method,¹⁸ described in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

The academic investigators and representatives of the sponsor, Novartis, designed the study and collected and analyzed the data. Drs. Kantarjian and Alland, who wrote the article with help from all the authors, vouch for the accuracy and completeness of the data and the analysis. All data were available to all investigators.

ASSESSMENT OF TOXIC EFFECTS AND RESPONSE

Complete blood counts and biochemical analysis were obtained weekly for the first eight weeks and then every other week. Bone marrow assessments were done on days 15 and 28 of the first cycle and on day 28 of every even-numbered cycle. Patients were evaluated for cytogenetic response at baseline and in repeated analyses if

they had a response. Safety assessments included an evaluation of adverse events, hematologic and cardiac-enzyme assessment, biochemical testing, urinalysis, electrocardiography, and physical examination.

Toxic effects were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). Criteria

Table 1. Characteristics of the Study Group.

Characteristic	Patients (N=119)	Characteristic	Patients (N=119)
Age — yr		Duration of nilotinib administration — mo	
Median	60	Chronic	
Range	15–83	Median	4.9
Female sex — no. (%)	62 (52)	Range	1.4–9.3
Presence of splenomegaly — no. (%)	32 (27)	Accelerated	
Hemoglobin <10 g/dl — no. (%)	40 (34)	Median	5.1
White-cell count >50,000/mm ³ — no. (%)	41 (34)	Range	0.3–12.6
Platelets <100,000/mm ³ — no. (%)	98 (82)	Accelerated, clonal evolution only	
Phase of CML — no. (%)		Median	5.0
Blastic		Range	0.1–9.6
Myeloid	24 (20)	Myeloid blastic	
Lymphoid	9 (8)	Median	2.9
Accelerated blastic		Range	0.4–10.7
Clonal evolution only	10 (8)	Lymphoid blastic	
Other accelerated criteria	46 (39)	Median	1.4
Chronic*		Range	0.9–9.7
Active disease	12 (10)	Highest previous daily dose of imatinib — mg	
Complete hematologic remission	5 (4)	Chronic	
Ph-positive ALL — no. (%)	13 (11)	Median	600
Duration of phase of CML — mo†		Range	400–800
Chronic		Accelerated	
Median	59.7	Median	800
Range	12.9–167.4	Range	400–1000
Accelerated		Accelerated, clonal evolution only	
Median	90.6	Median	600
Range	7.2–226.9	Range	400–800
Accelerated, clonal evolution only		Myeloid blastic	
Median	59.0	Median	600
Range	8.1–126.7	Range	400–800
Myeloid blastic		Lymphoid blastic	
Median	49.9	Median	600
Range	3.8–186.9	Range	400–800
Lymphoid blastic		Ph-positive ALL	
Median	19.4	Median	600
Range	3.2–82.9	Range	400–800
		Presence of baseline mutation in <i>BCR-ABL</i> — no./total no. (%)	41/91 (45)

* Patients with chronic-phase CML were enrolled in the study after the first four dose cohorts.

† The duration of disease was calculated from the date of the first diagnosis of CML to the date of the first administration of nilotinib.

with respect to hematologic and cytogenetic responses have been described previously.^{1,16,17,19-21} Cytogenetic responses were as follows (percentages refer to the percentage of Ph-positive metaphases): complete response, 0 percent; partial response, 1 to 35 percent; minor response, 36 to 65 percent; and minimal response, 66 to 95 percent.¹⁶ Response criteria among patients with Ph-positive ALL were described previously.^{5,20}

OTHER ANALYSES

Patients were evaluated for the inhibition of biomarker phosphorylation, the mutational status of BCR-ABL, and Gilbert's syndrome. The methods used in these analyses are detailed in the Supplementary Appendix.

RESULTS

PATIENTS

At three centers, from May 25, 2004, to May 4, 2005, we enrolled 119 patients whose disease was resistant to imatinib. The patients were assigned to receive daily doses of nilotinib according to the following dosing schedule: 50 mg (7 patients), 100 mg (7), 200 mg (10), 400 mg (10), 600 mg (6), 800 mg (19), and 1200 mg (10) or to receive 400 mg twice daily (32) or 600 mg twice daily (18). The characteristics of patients are shown in Table 1. As of June 15, 2005, 66 patients remained in the study, including all 17 patients with chronic-phase CML. Reasons for discontinuation included adverse events (8 patients), death during the study period (5), disease progression (35), and withdrawal of consent (5). Four patients who withdrew their consent underwent hematopoietic stem-cell transplantation.

PHARMACOKINETICS

The median time to peak concentrations of nilotinib was three hours after administration, and the mean peak concentration was 3.6 μM at steady state among patients receiving 400 mg twice daily. The apparent half-life of the drug was 15 hours. The steady-state level was achieved by day 8. The steady-state serum level of the drug was two to three times the level measured after the first dose. With the administration of daily doses at the steady-state level, the peak concentration and the area under the concentration-time curve increased among patients receiving 50 to 400 mg of the drug and reached a plateau among

patients receiving more than 400 mg. Considering that saturation may have been caused by gastrointestinal absorption, the dose was reduced to 400 mg twice daily and then was further escalated to 600 mg twice daily. Exposure at the steady-state level was greater with 400 mg twice daily than with a daily dose of 800 mg, and there was a dose-proportional increase in exposure between 400 mg twice daily and 600 mg twice daily (Fig. 1).

The mean serum trough level at the steady-state level was 1.0 μM at 400 mg daily, 1.7 μM at 400 mg twice daily, and 2.3 μM at 600 mg twice daily. All trough levels exceeded the 50 percent inhibitory concentration of cellular phosphorylation of BCR-ABL (20 to 57 nM, depending on cell type) and 32 of 33 BCR-ABL kinase mutants (19 to 709 nM).¹²

SAFETY PROFILE

No dose-limiting toxic effects were seen at doses of up to 600 mg daily. Dose-limiting toxic effects occurred among 18 patients at doses higher than 600 mg. Such effects included an elevation in bilirubin level (predominantly grade 3), mostly indirect bilirubin (nine patients); a grade 3 elevation

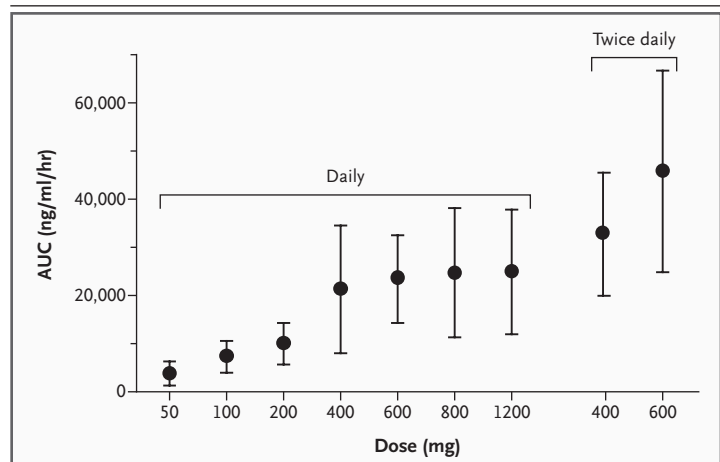


Figure 1. Total Steady-State Serum Levels of Nilotinib, According to the Daily Dose.

The graph shows the area under the concentration-time curve (AUC) during the first 24 hours after the first dose of nilotinib was administered, according to the total amount of drug patients received either once or twice daily. The points represent the mean levels of the drug, and the I bars represent the standard deviations. The total number of patients in whom levels were tested were as follows: 50 mg daily (3 patients), 100 mg daily (4 patients), 200 mg daily (3 patients), 400 mg daily (8 patients), 600 mg daily (4 patients), 800 mg daily (18 patients), and 1200 mg daily (8 patients), as well as 400 mg twice daily (30 patients) and 600 mg twice daily (18 patients).

in the aminotransferase level (three patients); a grade 4 elevation in the lipase level (one patient); a grade 3 or 4 elevation in amylase and lipase levels (two patients, one of whom had grade 2 pancreatitis); grade 4 hematologic toxic effects (two patients); and a grade 3 subdural hematoma (one patient). The method of continuous modified reassessment indicated that 600 mg administered twice daily is the maximum tolerated dose. (The posterior probability of dose-limiting toxicity was 0.30, which is discussed in the Supplementary Appendix.)

Table 2 presents a list of adverse events with an incidence of at least 4 percent that were potentially associated with nilotinib. Thrombocytopenia (21 percent) and neutropenia (14 percent) were mainly grade 3 or 4 and appeared to increase with increasing doses of the drug. Pruritus, rash, and dry skin were almost exclusively grade 1 or 2. When all categories of rash were combined, there appeared to be a dose-related increase in incidence.

Grade 3 elevations in levels of alanine aminotransferase and aspartate aminotransferase were infrequent and observed at daily doses of 600 mg or more. Elevations in total, conjugated, and unconjugated bilirubin levels accounted for 14 percent of adverse events. These increases were primarily in unconjugated bilirubin and were not accompanied by an increase in levels of aminotransferase or evidence of increased hemolysis; the increased levels often occurred during the first week of therapy. The frequency and grade of elevation in bilirubin levels increased with increasing amounts of nilotinib. Elevations frequently resolved spontaneously with continued administration of nilotinib. There was a positive correlation ($P=0.009$) between the presence of the (TA)₇/(TA)₇ sequence in the promoter regions of the gene encoding bilirubin uridine diphosphoglucuronate (UDP) glucuronosyltransferase 1A1, a genotype associated with Gilbert's syndrome,²² and the incidence of grade 3 or 4 elevations of total bilirubin levels, as well as a higher mean level of bilirubin. Among 14 patients with Gilbert's syndrome, 7 had elevations in bilirubin levels, as compared with 10 of 97 patients who did not have the syndrome.

A grade 3 elevation in the amylase level was reported in one patient, and six patients had grade 3 or 4 elevations in lipase levels; of those six patients, three reported having abdominal pain.

One of these patients (with a history of pancreatitis) had grade 2 pancreatitis. Among patients with available laboratory data, grade 3 or 4 elevations in lipase levels were seen in 9 of 55 patients (16 percent), and grade 3 elevations in amylase levels were seen in 3 of 57 patients (5 percent). All the increased levels were observed at daily doses of 600 mg or more.

In an exploratory analysis of more than 2200 electrocardiograms from 119 patients, the only abnormality associated with nilotinib was in the corrected QT interval by Fridericia's formula (QTcF), which appeared to increase by 5 to 15 msec in the study group. One patient had two adverse cardiac events associated with nilotinib, which included pericardial effusion (grade 1) and atrial fibrillation (grade 2), with no elevation in cardiac enzymes.

After the data cutoff for our study, two study patients died unexpectedly. One patient was a 30-year-old man with CML in complete remission; an autopsy confirmed an overdose of methadone. The other patient was a 56-year-old man with CML in an accelerated phase; there was no autopsy, and the cause of death was unknown.

RESPONSE

All patients in our study had disease that was resistant to imatinib. Overall, of 33 patients with the blastic phase, 13 had a hematologic response to nilotinib (39 percent) (Table 3) and 9 patients (27 percent) had a cytogenetic response, 6 of whom had a major cytogenetic response (Ph-positive cells in metaphase, ≤ 35 percent). Of 46 patients with accelerated-phase CML (excluding those with clonal evolution only), 33 had a hematologic response; 22 had a cytogenetic response, and 9 of those responses were major. Among the 10 patients who had clonal evolution as the only feature of the accelerated phase of CML, 5 had active disease and 5 were in complete hematologic remission. All 5 patients with clonal evolution and hematologic disease had a complete hematologic response; 6 of 10 had a major cytogenetic response (Table 3).

Table 4 shows the results in patients who had accelerated or blastic phases of disease who had a dose escalation owing to inadequate response at the initial dose level. Overall, 13 of 23 patients who were initially treated at daily doses of 50 to 400 mg had hematologic responses when they received 600 mg daily or 400 mg twice daily. At

Table 2. Adverse Events Reported by at Least 4 Percent of Patients.*

Adverse Event†	50–200 mg/Day (N=24)		400 mg/Day (N=10)		600–1200 mg/Day (N=35)		400 mg Twice Daily (N=32)		600 mg Twice Daily (N=18)		Any Dose (N=119)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
<i>percent of patients</i>												
Nonhematologic event												
Rash (all types)	17	0	10	0	20	3	22	0	28	6	20	2
Pruritus	21	0	10	0	17	0	6	3	22	6	15	2
Dry skin	13	0	10	0	17	0	6	0	11	0	12	0
Constipation	17	0	10	0	3	0	0	0	22	0	8	0
Nausea, vomiting, or both	8	0	0	0	6	0	13	0	6	0	8	0
Increase in both total and conjugated bilirubin levels	4	0	0	0	0	3	6	3	17	11	5	3
Fatigue	0	0	0	0	0	3	16	0	6	0	5	1
Increase in unconjugated bilirubin level	0	0	0	0	0	6	6	3	0	11	2	4
Alopecia	13	0	10	0	6	0	0	0	6	0	6	0
Increase in lipase level	0	0	0	0	0	3	0	9	0	11	0	5
Increase in level of ALT, AST, or both	0	0	0	0	0	9	3	3	0	0	1	3
Hematologic event												
Thrombocytopenia	0	13	0	20	0	17	3	25	0	28	1	20
Neutropenia	0	8	0	10	3	14	0	9	0	22	1	13
Anemia	0	4	0	10	9	6	0	6	0	6	3	6

* Safety data are presented by dividing patients into five groups on the basis of values in the area under the concentration–time curve as follows: group 1 (50, 100, and 200 mg daily), group 2 (400 mg daily), group 3 (600, 800, and 1200 mg daily), group 4 (400 mg twice daily), and group 5 (600 mg twice daily). Many patients received a higher dose of study drug than the dose they received in their initial cohort. The mean number of inpatient dose escalations (increases by 50 to 400 mg daily), ranged from 4.3 to 1.5. Therefore, in the first three groups of the initial-dose cohort, the patients in each group who reported having adverse events may actually have been receiving a higher dose than the amount indicated.

† Laboratory adverse events were reported only if they required therapy, constituted a serious adverse event, were clinically significant, or prompted withdrawal from the study. Other grade 3 or 4 adverse events reported by no more than 3 percent of patients were abdominal pain (3 percent); bone marrow depression, an increase in blood amylase level, and bone pain (2 percent); and febrile neutropenia, subdural or subarachnoid hemorrhage, musculoskeletal pain, and thrombosis (1 percent). ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

Table 3. Hematologic and Cytogenetic Responses.*

Variable	Total No. of Patients	Hematologic Response				Cytogenetic Response [†]					
		Active Disease [‡]	Complete Hematologic Response	Marrow Response	Return to Chronic Phase	Complete Response	Partial Response	Minor Response	Minimal Response	Major Response	Total
Transformed CML											
Accelerated phase											
Hematologic disease	46	46	21	3	9	6	3	4	9	9	22 (48)
Clonal evolution only [§]	10	5	5	NA	NA	2	4	1	2	6	9 (90)
Total	56	51	26	3	9	8	7	5	11	15	31 (55)
Blastic phase											
Myeloid	24	24	2	2	6	1	4	2	0	5	7 (29)
Lymphoid	9	9	0	1	2	1	0	0	1	1	2 (22)
Total	33	33	2	3	8	2	4	2	1	6	9 (27)
Chronic-phase CML	17	12	11	NA	NA	6	0	0	3	6	9 (53)

number of patients/total number (percent)

* NA denotes not applicable.

[†] The cytogenetic response was categorized as follows: complete response, no Ph-positive cells in the bone marrow; partial response, 1 percent to 35 percent Ph-positive cells; minor response, 36 percent to 65 percent Ph-positive cells; and minimal response, 66 percent to 95 percent Ph-positive cells.

[‡] Patients had active disease when they entered the study.

[§] The presence of clonal evolution is the only criterion for the accelerated-phase designation.

once-daily doses of 600 mg or more, less than 10 percent of patients required a dose escalation. Response rates at the twice-daily doses of 400 and 600 mg were similar.

Among 17 patients with the chronic phase of disease, the median duration of therapy was 4.9 months (range, 1.4 to 9.3), and all of the patients have continued therapy. At the present time, 11 of 12 patients with active disease have had a complete hematologic remission. There were cytogenetic responses in 9 of 17 patients who could be evaluated, including 6 responses that were complete (Table 3). Complete cytogenetic responses were noted in 3 of 12 patients who had hematologic disease at baseline and in 3 of 5 patients who were in complete hematologic remission at the start of therapy (Table 5).

One of 10 patients with Ph-positive ALL (hematologic relapse) had a partial hematologic response, and 1 of 3 patients with Ph-positive ALL and persistent molecular signs of ALL had a complete molecular remission.

SIGNALING MOLECULES

Phosphorylation of AKT, CRKL, STAT1, and STAT5 in all cells was compared at baseline and on day 15 in patients in blastic and accelerated phases of disease whose leukemic cells had phosphorylation of these proteins at baseline and who received 400 or 600 mg of nilotinib twice daily. In all four signaling molecules, there was significantly decreased phosphorylation on day 15 of nilotinib treatment, as compared with that at baseline after adjustment for multiple testing (overall significance level for all comparisons, 0.05). (See the section entitled “Assessment of Biomarker Inhibition” in the Supplementary Appendix.)

ABL MUTATIONS AND RESPONSE TO NILOTINIB

In about 50 percent of samples, a duplicate baseline sample was available for confirmatory analysis of ABL mutations by an academic laboratory; the concordance was 100 percent between the central and academic laboratories. A total of 51 ABL mutations were observed in 37 of 91 patients who had a baseline assessment for mutational status. Nilotinib was active in patients with and in those without mutations, but there were no significant differences in the response rates between the two groups. (See the section entitled “Assessment of BCR-ABL Mutational Status” in the Supplementary Appendix.) Two patients with a T315I muta-

Table 4. Dose Escalation and Hematologic Response in Patients with Accelerated and Blastic Phases of Disease.

Initial Nilotinib Dose	Phase of Disease	Patients in Dose Cohort	Patients Receiving Dose Escalation*	Best Hematologic Response with Dose Escalation
50–200 mg daily	Accelerated	9	8	400 mg daily: 3 patients with complete hematologic response; 1 patient with return to chronic phase 800 mg daily: 1 patient with return to chronic phase 400 mg twice daily: 1 patient with complete hematologic response
	Blastic	11	9	400 mg daily: 1 patient with return to chronic phase 800 mg daily: 2 patients with return to chronic phase
400 mg daily	Accelerated	4	3	400 mg twice daily: 1 patient with marrow response; 2 patients with complete hematologic response
	Blastic	3	3	600 mg daily: 1 patient with return to chronic phase

* Patients with an inadequate response to treatment received an escalation in the dose of nilotinib. A total of 4 of 45 patients in cohorts that received daily doses of nilotinib of 600 mg or more had an escalation in dose, and no responses were observed as a result of the escalations.

tion (one with chronic-phase CML and one with blastic-phase CML) had no response to nilotinib.

DISCUSSION

This phase 1 study of nilotinib defined the dose-limiting toxic effects and the maximum tolerated dose of the drug. We also report adverse events associated with treatment and an assessment of the activity of nilotinib in imatinib-resistant CML. We found that nilotinib has activity in imatinib-resistant CML, including in cases with mutations in the gene that encodes the ABL kinase that cause imatinib resistance.⁸⁻¹²

Imatinib therapy has side effects that can be dose-limiting in 10 percent of patients.²³ In this study, nilotinib was not associated with the common toxic effects seen with imatinib (e.g., fluid retention, edema, and weight gain) or with pleural effusions. Frequently noted side effects of nilotinib were mild-to-moderate rashes; transient, clinically insignificant elevations of indirect bilirubin levels; and myelosuppression, which was dose-related and dose-limiting. The method of continuous modified reassessment selected the twice-daily dose of nilotinib of 600 mg as the maximum tolerated dose, but the value of lower doses should be explored, since the 400-mg twice-daily dose appeared to have a response rate similar to that of the 600-mg twice-daily dose and

had a better safety profile. The incidence of grade 3 or 4 neutropenia was 22 percent with 600 mg twice daily and 9 percent with 400 mg twice daily; the incidence of increased indirect bilirubinemia was 11 percent with 600 mg twice daily and 3 percent with 400 mg twice daily. The recommended dose of nilotinib for phase 2 studies is 400 mg twice daily, with possible dose escalation to 600 mg twice daily in patients with an inadequate response.

Nilotinib has a serum half-life of 15 hours and thus was initially given as a single daily dose. However, saturation of serum levels was observed with this schedule at doses ranging from 400 to 1200 mg daily. When the schedule was modified to a twice-daily regimen, there were increases of 50 to 80 percent in peak serum levels and in levels in the area under the concentration–time curve at the same total daily dose of nilotinib (Fig. 1). At a steady-state level of twice-daily doses of 400 mg and 600 mg, there was a significant reduction in phosphorylation of AKT, CRKL, STAT1, and STAT5, as compared with levels at baseline.

The rates of hematologic response in patients with resistance to imatinib were 75 percent for patients with the accelerated phase and 39 percent for those with the blastic phase. Cytogenetic response rates in these two phases were 55 percent and 27 percent, respectively. The rate of

Table 5. Response to Nilotinib among Patients with Chronic-Phase CML, According to the Starting-Dose Cohort.*

Nilotinib Dose	Patients with Active Disease	Patients without Active Disease	Complete Hematologic Response†	Cytogenetic Response‡		
				Complete	Minimal	Total
<i>number of patients (percent)</i>						
400–1200 mg once daily	3	1	3 (100)	2 (50)	0	2 (50)
400 mg twice daily	5	3	5 (100)	3 (38)	2 (25)	5 (63)
600 mg twice daily	4	1	3 (75)	1 (20)	1 (20)	2 (40)
All doses	12	NA	11 (92)	3 (25)	2 (17)	5 (42)
	NA	5	NA	3 (60)	1 (20)	4 (80)

* NA denotes not applicable.

† The rate of complete hematologic response was determined by dividing the number of patients who had a complete hematologic response by the number of patients with active disease at baseline.

‡ No partial or minor cytogenetic responses were noted. The rate of cytogenetic response was determined by dividing the number of patients who had a cytogenetic response by the total number of patients.

complete hematologic response in patients with chronic-phase CML was 92 percent, and the rate of complete cytogenetic response was 35 percent. The disease of all these patients was resistant to imatinib (median dose, 800 mg).

Mutations in the gene that encodes the ABL kinase, a mechanism of resistance to imatinib, were noted in 45 percent of patients. In this study, response rates were similar in patients with and those without such mutations. Two patients with a mutation of T315I did not have a response to nilotinib, as predicted from preclinical studies.^{11,12} These findings suggest that nilotinib may overcome mutation-associated resistance to imatinib.

Our results in patients with Ph-positive ALL who did not have a response to imatinib suggest that nilotinib has limited efficacy in this subgroup, since only 2 of 13 such patients had a response to the drug. Therefore, nilotinib may have a limited role in patients with Ph-positive ALL.

We found that nilotinib prolongs the QTcF interval in some patients. One unexplained sudden death was reported beyond the follow-up time analysis. This finding indicates the need for careful monitoring for cardiac events and arrhyth-

mias in all patients who are receiving nilotinib and a strict avoidance of medications that may prolong the QTcF interval.

In summary, nilotinib has a relatively favorable safety profile, and preliminary results obtained with a relatively short follow-up period indicate that the drug is active in CML. Phase 2 studies of nilotinib and other BCR-ABL inhibitors, such as dasatinib,²⁴ are ongoing in patients with CML.

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