ACTIVITY OF A SPECIFIC INHIBITOR OF THE BCR-ABL TYROSINE KINASE IN THE BLAST CRISIS OF CHRONIC MYELOID LEUKEMIA AND ACUTE LYMPHOBLASTIC LEUKEMIA WITH THE PHILADELPHIA CHROMOSOME

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ABSTRACT

Background BCR-ABL, a constitutively activated tyrosine kinase, is the product of the Philadelphia (Ph) chromosome. This enzyme is present in virtually all cases of chronic myeloid leukemia (CML) throughout the course of the disease, and in 20 percent of cases of acute lymphoblastic leukemia (ALL). On the basis of the substantial activity of the inhibitor in patients in the chronic phase, we evaluated STI571 (formerly known as CGP 57148B), a specific inhibitor of the BCR-ABL tyrosine kinase, in patients who had CML in blast crisis and in patients with Ph-chromosome–positive ALL.

Methods In this dose-escalating pilot study, 58 patients were treated with STI571; 38 patients had myeloid blast crisis and 20 had ALL or lymphoid blast crisis. Treatment was given orally at daily doses ranging from 300 to 1000 mg.

Results Responses occurred in 21 of 38 patients (55 percent) with a myeloid-blast-crisis phenotype; 4 of these 21 patients had a complete hematologic response. Of 20 patients with lymphoid blast crisis or ALL, 14 (70 percent) had a response, including 4 who had complete responses. Seven patients with myeloid blast crisis continue to receive treatment and remain in remission from 101 to 349 days after starting the treatment. All but one patient with lymphoid blast crisis or ALL has relapsed. The most frequent adverse effects were nausea, vomiting, edema, thrombocytopenia, and neutropenia.

Conclusions The BCR-ABL tyrosine kinase inhibitor STI571 is well tolerated and has substantial activity in the blast crises of CML and in Ph-chromosome–positive ALL. (N Engl J Med 2001;344:1038-42.)

THE BCR-ABL tyrosine kinase, the product of the chimeric gene produced by the Philadelphia (Ph) chromosome, is the molecular abnormality that causes chronic myeloid leukemia (CML). During the chronic phase of the disease, there is massive clonal expansion of myeloid cells, which retain the ability to differentiate. Over time, however, the leukemic clone loses this ability, and the disease inevitably progresses to an acute leukemia known as blast crisis.[1,2] In two thirds of patients the blasts are myeloid, and in one third they are lymphoid. Up to 20 percent of adults and 5 percent of children with acute lymphoblastic leukemia (ALL) have the BCR-ABL fusion protein.[1] In virtually all patients with CML, including those with blast crisis, the BCR-ABL protein has a molecular mass of 210 kd, whereas in 50 percent of adults and 80 percent of children with ALL the BCR-ABL protein is smaller, with a molecular mass of 185 or 190 kd.[1,2]

The blast crisis is highly refractory to treatment. The rate of response to standard induction chemotherapy in patients with myeloid blast crisis is approximately 20 percent, and the rate of complete remission is less than 10 percent. In patients with lymphoid blast crisis, the rate of response is approximately 50 percent, but remissions are short-lived.[3-5] After allogeneic stem-cell transplantation during blast crisis, the five-year survival rate is only 6 percent[6,7]; Ph-chromosome–positive ALL also has a poor prognosis.[8-10]

STI571 (4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide methanesulfonate; Glivec, Novartis, Basel, Switzerland) is a potent and selective inhibitor of the tyrosine kinase activity of BCR-ABL.[11,12] In a phase 1 trial of STI571 in patients with CML in the chronic phase, reported elsewhere in this issue of the *Journal,* those treated with daily doses of 300 mg or more had a high rate of response and minimal adverse effects.[13] Disease progression to blast crisis is associated with genetic instability and numerous molecular abnormalities. Thus, it is possible that other oncogenic abnormalities replace the need for BCR-ABL tyrosine kinase activity for cellular survival of leukemic blasts. In this study, we evaluated the effects of STI571 in the treatment of CML in blast crisis and Ph-chromosome–positive ALL.

METHODS

Patients

Patients with CML were eligible if they tested positive for the Ph chromosome, were at least 18 years of age, and were in blast crisis (with more than 30 percent blasts in the peripheral blood or bone marrow), irrespective of prior therapy. Patients with Ph-chromosome–positive ALL were eligible if they had not had a response to standard induction or consolidation chemotherapy or had had a relapse after such therapy. Treatment with STI571 was not initiated until at least 24 hours after treatment with hydroxyurea ended and until at least four weeks after treatment with standard induction or consolidation therapy ended. Adequate renal, hepatic, and cardiac function and performance status were required.

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Written informed consent was obtained from all patients before they entered the study.

Study Design

This pilot dose-escalation study was designed to assess the antileukemic activity and safety of STI571 in patients with CML in blast crisis or Ph-chromosome–positive ALL. Patients were assigned to successive dose cohorts of STI571 ranging from 300 to 1000 mg. The starting dose of 300 mg per day was selected on the basis of its efficacy in a parallel phase 1 study in patients with CML in the chronic phase.[13] To dissociate the confounding role of underlying illness in acutely ill patients from drug-related toxicity, decisions about dose escalation were based on findings from the phase 1 study, which was conducted simultaneously. Six to eight patients were assigned to each dose; STI571 was administered orally once daily, except for the 800-mg and 1000-mg doses, which were administered twice daily in 400-mg and 500-mg doses, respectively. Patients received continuous therapy unless unacceptable adverse effects or disease progression occurred. Therapy with hydroxyurea was permitted after the initiation of treatment for a maximum of seven days during the first four weeks as required to maintain acceptable blood counts. No other anticancer agents were allowed during treatment, and no dose modifications were allowed for hematologic toxicity during the first 14 days of therapy. All patients received allopurinol for 48 hours before the initiation of treatment with STI571.

Complete blood counts were obtained three times weekly. Assessments of bone marrow, including cytogenetic assessments, were performed once every 6 weeks during the first 12 weeks of treatment and then once every 12 weeks. If grade 4 neutropenia, defined as an absolute neutrophil count of less than 500 per cubic millimeter, occurred on or after 14 days of treatment with STI571, bone marrow aspiration and biopsy were performed. If marrow cellularity was less than 10 percent, treatment with STI571 was interrupted until the absolute neutrophil count rose to more than 1000 per cubic millimeter. If neutropenia recurred, treatment with STI571 was again interrupted until the absolute neutrophil count was more than 1000 per cubic millimeter and then resumed at the dose level of the previous cohort. If marrow cellularity was more than 10 percent, contained more than 30 percent blasts, or both, treatment with STI571 was continued. There were no dose modifications for thrombocytopenia.

Assessment of Toxicity and Response

Safety assessments included the evaluation of adverse events and vital signs, hematologic tests, biochemical tests, urinalysis, and physical examination. Toxicity was graded in accordance with the Common Toxicity Criteria of the National Cancer Institute.[14]

We used standard criteria to define a complete hematologic response[4]: a decrease in marrow blasts to 5 percent or less of total cellularity, a disappearance of blasts from the peripheral blood, an absolute neutrophil count of more than 1000 per cubic millimeter, and a platelet count of more than 100,000 per cubic millimeter. In patients who did not have a complete hematologic response, a marrow response was defined as a decrease in marrow blasts to either no more than 5 percent or between 5 and 15 percent, regardless of the peripheral-blood cell counts. A relapse was defined as either disease progression (an increase in marrow blasts to more than 15 percent, in peripheral-blood blasts to more than 5 percent, or in white cells to more than 20,000 per cubic millimeter) or death. The time to relapse was calculated from the first dose of STI571. Cytogenetic responses were classified as previously described.[4]

RESULTS

Accrual of Patients

From April 1999 through March 2000, 58 patients were enrolled; their characteristics are summarized in Table 1. Patients with lymphoid blast crisis and Ph-chromosome–positive ALL are grouped together. The phenotype of the blasts in the 58 patients was myeloid in 38 and lymphoid in 20; these 20 included 10 patients with Ph-chromosome–positive ALL. One patient was enrolled as an exception, on the basis of lymphoid blasts in the breast that were detected during the course of CML. Sixteen patients with myeloid blast crisis and seven with lymphoid blast crisis had received previous therapy for the blast crises. The study required that all patients with Ph-chromosome–positive ALL had received prior chemotherapy. The study is ongoing, and the results reported here represent an interim analysis of the data.

TABLE 1. CHARACTERISTICS OF THE 58 PATIENTS.

CHARACTERISTIC	VALUE
Sex — M/F	35/23
Age — yr	
Median	48
Range	24–76
History of disease — no. (%)	
Myeloid blast crisis	38 (66)
Lymphoid blast crisis	10 (17)
Ph-chromosome–positive ALL	10 (17)
Previous therapy for acute leukemia — no. (%)	
Patients with myeloid blast crisis	16 (42)
Patients with lymphoid blast crisis	7 (70)
Additional cytogenetic abnormalities — no. (%)	
Patients with myeloid blast crisis	22 (58)
Patients with lymphoid blast crisis or ALL	13 (65)
White-cell count at base line — cells/mm^3	
Median	25,200
Range	100–171,000
Platelet count at base line — cells/mm^3	
Median	92,000
Range	4,000–1,278,000

TABLE 2. DRUG-RELATED ADVERSE EFFECTS.*

ADVERSE EFFECT	GROUP RECEIVING 300 mg/DAY (N=8)		GROUP RECEIVING 400–500 mg/DAY (N=17)		GROUP RECEIVING 600–1000 mg/DAY (N=33)		TOTAL (N=58)
	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADES 1–4
	percentage of patients						no. (%)
Nausea	25	12	35	6	55	12	32 (55)
Vomiting	38	0	35	6	33	9	24 (41)
Edema	25	12	18	6	45	6	24 (41)
Myalgia	25	0	18	0	21	0	12 (21)
Diarrhea	0	0	12	0	24	0	10 (17)
Rash	0	0	18	0	15	6	10 (17)
Fatigue	12	0	24	0	3	0	6 (10)
Anorexia	12	0	18	0	6	0	6 (10)

*The adverse effects listed here were considered to be related to STI571 and were reported in more than 10 percent of patients. A grade of 1 indicates mild adverse effects, a grade of 2 moderate effects, a grade of 3 severe effects, and a grade of 4 life-threatening effects.

Safety Profile

STI571 was generally well tolerated (Table 2). The most frequent adverse effects were nausea (in 55 percent of patients), vomiting (41 percent), and edema (41 percent); most of these were grade 1 (mild) or grade 2 (moderate). Patients treated with higher doses of STI571 were more likely to have grade 1 or 2 nausea, edema, or diarrhea than patients given lower doses of the drug. Grade 4 neutropenia and thrombocytopenia occurred in 40 percent and 33 percent of patients, respectively (Table 3). Elevations in liver-enzyme levels of grade 3 or 4 were reported in eight patients (14 percent) a median of 16 days after the initiation of treatment (range, 7 to 194), without evidence of a dose relation. Treatment with STI571 was discontinued because of these abnormalities in only one patient; four of the eight patients had grade 1 elevations in liver-enzyme levels at base line.

There were 16 deaths due to disease progression. No deaths were considered to be related to treatment with STI571. The following serious adverse events in 13 patients were possibly related to STI571: nausea and vomiting in 4 patients, febrile neutropenia in 3 patients, and elevated liver-enzyme levels, exfoliative dermatitis, gastric hemorrhage, renal failure, pancytopenia, and congestive heart failure in 1 patient each. These events occurred more frequently in patients treated with 800 or 1000 mg of STI571 per day.

Hematologic and Bone Marrow Response

In the intention-to-treat analysis of response rates, all patients in the study were included whether or not the response could be properly evaluated. There was a decrease of 50 percent or more in peripheral-blood blasts in 46 of the 58 patients (79 percent). According to the criteria for responses described in the Methods section, the overall rates of response were 55 percent and 70 percent among patients with myeloid and lymphoid blast crises, respectively (Tables 4 and 5). Of the 38 patients with myeloid blast crisis, 4 had a complete hematologic remission and 17 had a decrease in blasts in the marrow to 15 percent or less (8 of these had a decrease to 5 percent or less). Of the 20 patients with lymphoid blast crisis and Ph-chromosome–positive ALL, 4 had a complete hematologic remission and 10 had a marrow response. In the small groups we studied, there was no relation between the dose of STI571 and the proportion of patients with hematologic responses. In patients who had a response to the drug, the reduction in peripheral blasts typically occurred within one week after the initiation of therapy (Fig. 1).

The median duration of therapy was 74 days (range, 1 to 349). Of the 21 patients with myeloid blast crisis who had a response to STI571, 9 subsequently relapsed between 42 and 194 days (median, 84) after the initiation of treatment. Seven of the 21 patients with myeloid blast crisis continue to receive therapy

TABLE 3. HEMATOLOGIC TOXICITY.*

VARIABLE	GROUP RECEIVING 300 mg/DAY (N=8)	GROUP RECEIVING 400–500 mg/DAY (N=17)	GROUP RECEIVING 600–1000 mg/DAY (N=33)	TOTAL (N=58)
	percentage of patients			
Neutropenia				
Grade 3	38	29	21	26
Grade 4	38	47	36	40
Thrombocytopenia				
Grade 3	38	35	36	36
Grade 4	25	29	36	33

*The lowest values reported during the study are listed. A grade of 1 indicates mild adverse effects, a grade of 2 moderate effects, a grade of 3 severe effects, and a grade of 4 life-threatening effects.

TABLE 4. RESPONSES IN PATIENTS WITH A MYELOID PHENOTYPE.

DOSE OF STI571 (mg/DAY)	NO. OF PATIENTS	NO. WITH COMPLETE HEMATOLOGIC RESPONSE	NO. WITH MARROW RESPONSE	
			≤5% BLASTS	6% TO ≤15% BLASTS
300	6	0	1	1
400	4	1	0	1
500	5	1	1	2
600	8	0	2	1
750	7	2	1	2
800	7	0	3	1
1000	1	0	0	1
Total — no. (%)	38	4 (11)	8 (21)	9 (24)

TABLE 5. RESPONSES IN PATIENTS WITH A LYMPHOID PHENOTYPE.

DOSE OF STI571 (mg/DAY)	NO. OF PATIENTS	NO. WITH COMPLETE HEMATOLOGIC RESPONSE	NO. WITH MARROW RESPONSE	
			≤5% BLASTS	6% TO ≤15% BLASTS
300	2	0	1	0
400	4	0	2	1
500	4	1	0	1
600	2	1	0	1
750	2	0	1	0
800	1	0	1	0
1000	5	2	2	0
Total — no. (%)	20	4 (20)	7 (35)	3 (15)

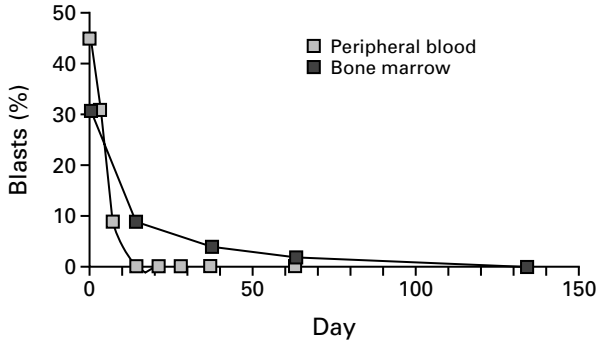

Figure 1. Kinetics of Complete Response in a Patient with Myeloid Blast Crisis Treated with 400 mg per Day of STI571.

and are in remission, with a follow-up of 101 to 349 days. The other five patients were removed from the study: one for hematopoietic stem-cell transplantation, one because of poor compliance with therapy, and three because of adverse events.

Of the 14 patients with lymphoid blast crisis who had a response to STI571, 12 relapsed a median of 58 days after the initiation of treatment (range, 42 to 123), 1 underwent hematopoietic stem-cell transplantation, and the data on 1 who was in remission at day 58 have been censored because of the short length of follow-up (Fig. 2). The patient with extramedullary disease had a complete response at the extramedullary site and remains in remission at day 243.

All patients who relapsed remained Ph-chromosome–positive. Major cytogenetic responses were observed in 7 of the 58 patients (12 percent). Of these responses, five were complete (three in patients with myeloid and two in patients with lymphoid blast crises) and two were partial, defined as less than 35 percent Ph-chromosome–positive cells (one in a patient with lymphoid and one in a patient with myeloid blast crisis).

DISCUSSION

This study demonstrates that STI571 as a single agent is well tolerated and has substantial activity against acute leukemias characterized by the BCR-ABL fusion protein. The overall response rate in the myeloid blast crisis of CML was 55 percent, and the rate of complete remission was 11 percent. Leukemic blasts in the marrow were reduced to 5 percent or less in 12 patients (32 percent). Of these 12 patients with myeloid blast crisis who initially had a response to STI571, 7 are still in remission after 101 to 349 days of follow-up.

There was no obvious difference in response rates or the durability of responses between patients with lymphoid blast crisis and those with Ph-chromosome–positive ALL. The overall response rate in patients with lymphoid blast crisis or Ph-chromosome–positive ALL was 70 percent, and 20 percent had complete remissions. A decrease in bone marrow blasts to 5 percent or less occurred in 11 patients (55 percent). However, all but one patient who had only extramedullary disease relapsed. With standard therapy, patients with lymphoid blast crisis have higher rates and greater durability of response than those with myeloid blast crisis. However, in this study, there was a trend toward a more durable response in the group of patients with myeloid blast crisis.

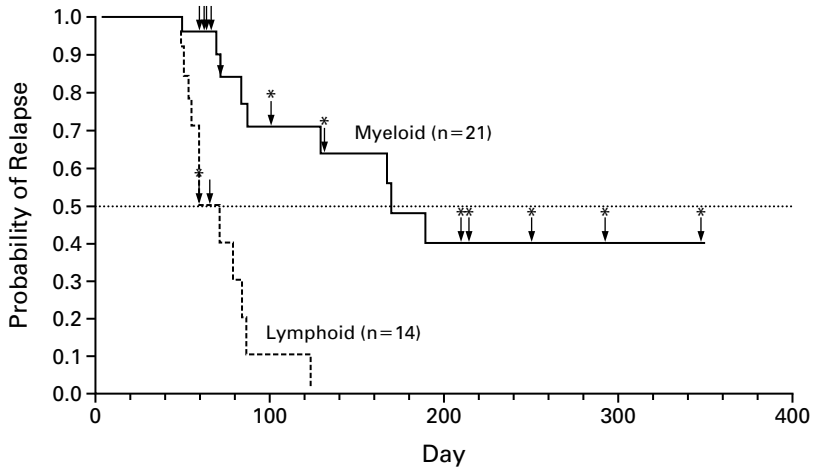

Figure 2. Time to Relapse in Patients with Myeloid or Lymphoid Blast Crisis Who Had a Response to STI571.

Arrows with asterisks indicate patients still enrolled in the study and in remission at the time of the last follow-up; arrows without asterisks indicate the day on which patients were removed from the study.

Since the outcome of hematopoietic stem-cell transplantation is better in patients with blast crisis who are first returned to the chronic phase of CML than in patients who undergo transplantation during blast crisis,[15] the reduction in the proportion of blasts in the marrow of patients with blast crisis suggests that STI571 may be a useful bridge to transplantation. Combinations of STI571 with standard antileukemic agents may also improve the outcome for patients with blast crisis.[16,17] In the patients with blast crisis we treated, STI571 had relatively few adverse effects, the most frequent of which were nausea, vomiting, and edema. There was some evidence of an increased incidence of toxic effects at the higher doses of STI571, especially at 800 to 1000 mg per day. Myelosuppression of grade 3 or 4 was more frequent in these patients with blast crisis than in patients with CML in the chronic phase who were treated with STI571 in a parallel phase 1 study.[13] This difference may reflect the severely compromised bone marrow function in patients in blast crisis and the fact that severe myelosuppression was allowed in this study because of the life-threatening nature of the illness, but not in the trial involving patients with CML in the chronic phase.

Rapid response is also a feature of therapy with STI571 (Fig. 1); despite this, the tumor lysis syndrome developed in only one patient. Preliminary data suggest that cells from treated patients undergo rapid apoptosis (data not shown). Although STI571 can be given to outpatients, careful monitoring during the initiation of therapy, vigorous hydration, and administration of allopurinol are recommended.

The mechanism of resistance to STI571 or relapse during treatment with the drug is a subject of intense interest. Analyses of blast-crisis CML cell lines that have acquired resistance to STI571 after prolonged culture in doses below the threshold for inhibition of growth[18-20] have shown amplification of the BCR-ABL gene, increased expression of the BCR-ABL protein without amplification of the gene, and increased expression of the multidrug-resistance protein (MDR1).[18-20] Preliminary analyses have shown that leukemic cells in patients who relapse retain the Ph chromosome and that serum levels of STI571 are unchanged at the time of relapse. These data are consistent with the in vitro data that implicate drug efflux or amplification of the BCR-ABL gene in resistance to STI571, but other mechanisms are also possible.[18-20]

This study clearly demonstrates that in the majority of patients with CML in blast crisis and Ph-chromosome–positive ALL, the leukemic clone remains at least partially dependent on BCR-ABL for survival. We also show that targeting a critical molecular abnormality, even in advanced stages of disease, is a useful strategy; however, in these cases it is likely that this agent will need to be combined with other therapies to achieve maximal therapeutic benefits.

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