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## HEMATOLOGIC AND CYTOGENETIC RESPONSES TO IMATINIB MESYLATE IN CHRONIC MYELOGENOUS LEUKEMIA

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### ABSTRACT

**Background** Chronic myelogenous leukemia (CML) is caused by the BCR-ABL tyrosine kinase, the product of the Philadelphia chromosome. Imatinib mesylate, formerly STI571, is a selective inhibitor of this kinase.

**Methods** A total of 532 patients with late–chronic-phase CML in whom previous therapy with interferon alfa had failed were treated with 400 mg of oral imatinib daily. Patients were evaluated for cytogenetic and hematologic responses. Time to progression, survival, and toxic effects were also evaluated.

**Results** Imatinib induced major cytogenetic responses in 60 percent of the 454 patients with confirmed chronic-phase CML and complete hematologic responses in 95 percent. After a median follow-up of 18 months, CML had not progressed to the accelerated or blast phases in an estimated 89 percent of patients, and 95 percent of the patients were alive. Grade 3 or 4 nonhematologic toxic effects were infrequent, and hematologic toxic effects were manageable. Only 2 percent of patients discontinued treatment because of drug-related adverse events, and no treatment-related deaths occurred.

**Conclusions** Imatinib induced high rates of cytogenetic and hematologic responses in patients with chronic-phase CML in whom previous interferon therapy had failed. (N Engl J Med 2002;346:645-52.)

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translocation of regions of the *BCR* and *ABL* genes to form a *BCR-ABL* fusion gene.<sup>1,7-12</sup> In at least 90 percent of cases, this event is a reciprocal translocation termed t(9;22), which forms the Philadelphia (Ph) chromosome.<sup>7,8</sup> The product of the *BCR-ABL* gene, the BCR-ABL protein, is a constitutively active protein tyrosine kinase with an important role in the regulation of cell growth.<sup>1,7</sup>

CML is potentially curable with allogeneic stem-cell transplantation, but fewer than 30 percent of patients have suitably matched donors.<sup>1,3,7,13</sup> Treatment with interferon alfa can induce a complete cytogenetic response in 5 to 20 percent of patients and result in longer survival than that achievable with chemotherapy, but it is associated with serious toxic effects.<sup>1,3,13-15</sup> Patients in whom interferon therapy fails are usually treated with hydroxyurea, busulfan, or investigational agents. The rate of hematologic response with these second-line agents is approximately 50 percent, but cytogenetic responses are uncommon. Furthermore, the rate of response decreases rapidly as the time from the initial diagnosis to the initiation of second-line therapy increases, particularly when such therapy is started in the late chronic phase, defined as more than 12 months after the initial diagnosis.

Imatinib mesylate (Gleevec, Novartis, Basel, Swit-

**C**HRONIC myelogenous leukemia (CML) accounts for about 20 percent of newly diagnosed cases of leukemia in adults.<sup>1,2</sup> The course of the disease is characteristically triphasic: a chronic phase lasting three to six years is followed by transformation to accelerated and then blast phases of short duration.<sup>1-6</sup> The cause of CML is the

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zeland), formerly called STI571, is a potent and selective competitive inhibitor of the BCR-ABL protein tyrosine kinase.<sup>16-20</sup> In a phase 1 dose-escalation study, daily doses of 300 mg or more of imatinib induced durable hematologic responses in nearly all patients with chronic-phase CML with minimal toxic effects.<sup>21</sup> Activity was also observed in patients whose CML was in the blastic phase.<sup>22</sup> We conducted this phase 2 study to characterize the efficacy and safety profiles of imatinib in a large group of patients with chronic-phase CML in whom previous interferon therapy had failed.

## METHODS

### Study Patients

Patients were eligible for the study if they were 18 years of age or older and had chronic-phase, Ph-chromosome-positive CML that had failed to respond to interferon therapy according to one of the criteria described below. The chronic phase was defined by the presence of less than 15 percent blasts, less than 20 percent basophils, and less than 30 percent blasts plus promyelocytes in the peripheral blood and marrow and a platelet count of at least 100,000 per cubic millimeter. Hematologic failure was defined as either hematologic resistance (failure to achieve a complete hematologic response after at least six months of interferon treatment) or relapse after a complete hematologic response had been achieved, with white-cell counts increased to at least 20,000 per cubic millimeter during interferon therapy. Whether they had hematologic or cytogenetic failure, patients were allowed to receive hydroxyurea for up to 50 percent of the duration of interferon treatment. Cytogenetic failures were defined as either cytogenetic resistance (at least 65 percent of cells in metaphase were Ph-chromosome-positive after at least one year of interferon therapy), or relapse after a major cytogenetic response had been achieved. A relapse was considered to have occurred if the proportion of Ph-chromosome-positive cells in metaphase increased by at least 30 percent or to at least 65 percent. Intolerance of interferon was defined by the presence of any nonhematologic toxic effect of grade 3 or higher (as defined by the National Cancer Institute Common Toxicity Criteria, in which a grade of 0 indicates no adverse effects and a grade of 5 life-threatening effects) that persisted for more than one month during therapy with interferon at a dose of 25 million units or more per week.

Patients were required to have levels of liver aminotransferases, serum bilirubin, and serum creatinine that were no higher than twice the upper limit of normal. Women with childbearing potential were required to have a negative pregnancy test before starting treatment, and all patients at risk were required to use barrier contraceptive measures. Patients were excluded from the study if their Eastern Cooperative Oncology Group performance score was 3 or higher (poor), or if they were in New York Heart Association functional class III or IV. Patients were excluded if they had received treatment with hydroxyurea within 7 days, interferon or cytarabine within 14 days, or any other investigational agent within 28 days before starting the study treatment.

All patients gave written informed consent according to institutional regulations. The study was performed in accordance with the Declaration of Helsinki.

### Study Design and Treatment

In this single-group multicenter, phase 2 trial, patients received imatinib in a daily oral dose of 400 mg. An increase to 400 mg twice daily was permitted in patients in whom a complete hematologic response had not been achieved after 3 months of treatment, those

whose disease relapsed within 3 months after the achievement of a complete hematologic response, and those in whom a major cytogenetic response had not been achieved after 12 months of therapy.

The study was designed by the investigators and representatives of the sponsor, Novartis. The data were collected with the data management and statistical support systems of Novartis and analyzed and interpreted by a statistician from Novartis in close collaboration with all the investigators. All academic investigators had access to the data. The paper was written by a committee consisting of Drs. Kantarjian, Sawyers, and Druker, along with three Novartis employees (Resta, Capdeville, and Zoellner). All academic authors received grant support from Novartis for the conduct of the study. Cytogenetic studies were performed at the cytogenetic laboratories of the individual investigators, and were centrally reviewed and audited by employees of Novartis.

### Dose Modifications because of Side Effects

If grade 2 nonhematologic toxic effects occurred and did not resolve during treatment, therapy was interrupted until the effects had been ameliorated to grade 1 or better and then resumed at the original dose. If grade 2 toxic effects recurred, treatment was again interrupted until the effects had been ameliorated to grade 1 or better and then resumed at a reduced daily dose of 300 mg. If grade 3 or 4 nonhematologic toxic effects occurred, therapy was interrupted until the effects had been ameliorated to grade 1 or better and then resumed at the reduced daily dose of 300 mg. If a patient had a grade 3 or 4 hematologic toxic effect (a neutrophil count of less than 1000 per cubic millimeter, or a platelet count of less than 50,000 per cubic millimeter), therapy was interrupted until the effect was ameliorated to grade 2 or better and then resumed at the same dose if the effect had reached the grade 2 level within two weeks and at a reduced daily dose of 300 mg if it had persisted at grade 3 or 4 for more than two weeks. Patients with anemia received blood transfusions at the discretion of the investigator.

Anticancer drugs were not administered concomitantly. Treatments with anagrelide or leukapheresis were permitted during the first three weeks of the study treatment.

### Evaluation of Patients

A complete blood count and a differential blood count were obtained weekly for the first 12 weeks, every other week for the next 12 weeks, and every 6 weeks thereafter. Bone marrow morphology and cytogenetics were evaluated every 12 weeks, when extramedullary involvement was also evaluated by physical examination. Adverse effects were evaluated at each visit and graded according to the National Cancer Institute Common Toxicity Criteria.

The primary efficacy end point was the rate of major cytogenetic response, which was categorized as either complete (0 percent Ph-chromosome-positive cells in metaphase in bone marrow) or partial (1 to 35 percent Ph-chromosome-positive cells in metaphase). Other categories of cytogenetic response were minor response (36 to 65 percent Ph-chromosome-positive cells in metaphase), minimal response (66 to 95 percent Ph-chromosome-positive cells in metaphase), and no response (more than 95 percent Ph-chromosome-positive cells in metaphase). Evaluation of the cytogenetic response was based on the examination of at least 20 cells in metaphase in marrow samples.

Secondary efficacy end points were the rate of complete hematologic response, the time to progression, and overall survival. Complete hematologic response was defined by a white-cell count of less than 10,000 per cubic millimeter, a platelet count of less than 450,000 per cubic millimeter, the presence of less than 5 percent myelocytes and metamyelocytes and less than 20 percent basophils in peripheral blood, the absence of blasts and promyelocytes in peripheral blood, and the absence of extramedullary involvement. Accelerated-phase CML was defined by the presence of 15 to 29 percent blasts in blood or marrow, the presence of at least 30 per-

cent blasts plus promyelocytes in blood or marrow, or the presence of at least 20 percent basophils in blood. Blast-phase CML was defined by the presence of at least 30 percent blasts in blood or marrow or the presence of extramedullary blastic disease. Time to progression was defined as the time from the start of treatment to the onset of an accelerated or blastic phase, discontinuation of therapy because of unsatisfactory therapeutic effect, or death. Survival was calculated from the beginning of therapy until the time of death from any cause.

**Statistical Analysis**

We aimed to demonstrate a major cytogenetic response rate of at least 20 percent among patients with previous hematologic failure and at least 30 percent among those with previous cytogenetic failure. On the basis of a Fleming procedure for single-stage, single-group testing (one-sided alpha, 0.025; power, 90 percent), sample sizes of at least 132 patients with previous hematologic failure and 79 with previous cytogenetic failure were considered necessary. Al-

lowing for withdrawals, the sample size was set at 150 patients with previous hematologic failure and 100 patients with previous cytogenetic failure. In addition, we anticipated enrollment of up to 100 patients with an intolerance to interferon, so that we could study the activity of imatinib in this population of patients. Patients who discontinued treatment before a response was reported were counted as not having had a response. Time to progression and survival were computed with the use of standard Kaplan–Meier methods.

Univariate and multivariate analyses were performed to test the associations between potential prognostic factors and a major cytogenetic response. The chi-square test was used to identify factors with prognostic value at a significance level of less than 0.2; these factors were then included as terms in a multivariate regression model. Factors whose association with major cytogenetic response was not significant at a level of less than 0.1 in multivariate analysis were removed; those remaining in the multivariate model were interpreted as independently predictive of major cytogenetic response.

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\***

VARIABLE	PATIENTS WITH CONFIRMED DIAGNOSIS OF CHRONIC-PHASE CML				ALL ENROLLED PATIENTS (N=532)
	ALL PATIENTS (N=454)	PATIENTS WITH HEMATOLOGIC FAILURE OF INTERFERON TREATMENT (N=133)	PATIENTS WITH CYTOGENETIC FAILURE OF INTERFERON TREATMENT (N=160)	PATIENTS WITH INTOLERANCE OF INTERFERON (N=161)	
Age					
Median — yr	57	56	53	60	57
Range — yr	18–81	18–79	24–77	25–81	18–90
≥60 yr — no. (%)	182 (40)	53 (40)	48 (30)	81 (50)	211 (40)
Sex — no.					
Male	270	90	96	84	311
Female	184	43	64	77	221
ECOG status — no. (%)					
0–1	423 (93)	127 (95)	148 (92)	148 (92)	488 (92)
2	14 (3)	5 (4)	2 (1)	7 (4)	18 (3)
Enlarged spleen ≥10 cm below the costal margin — no. (%)	10 (2)	3 (2)	4 (2)	3 (2)	12 (2)
Enlarged liver ≥5 cm below the costal margin — no. (%)	6 (1)	3 (2)	1 (1)	2 (1)	8 (2)
Lymph-node involvement — no. (%)	0	0	0	0	11 (2)
Extramedullary disease — no. (%)	0	0	0	0	1 (0.2)
White-cell count — per cubic millimeter					
Median	15,000	29,000	12,000	12,000	14,000
Range	2000–260,000	3000–260,000	2000–255,000	2000–173,000	2000–260,000
Platelet count — per cubic millimeter					
Median	303,000	375,000	272,000	321,000	296,000
Range	100,000–2,081,000	102,000–1,726,000	100,000–1,220,000	101,000–2,081,000	75,000–2,081,000
Hemoglobin level — g/dl					
Median	12.5	12.4	12.4	12.5	12.4
Range	7.3–17.2	8.7–16.6	7.3–17.2	8.8–16.6	7.3–17.2
Basophils — %					
Median	2	3	2	2	2
Range	0–16	0–16	0–15	0–14	0–23
Time since diagnosis — mo					
Median	34	34	33	34	32
Range	3–218	3–131	12–184	3–218	3–218
Duration of previous interferon therapy — mo					
Median	14	13	22	7	14
Interquartile range	7–28	7–27	14–42	3–14	7–27

\*Data on Eastern Cooperative Oncology Group (ECOG) status were missing for 17 patients. CML denotes chronic myelogenous leukemia.

**RESULTS**

**Patients and Treatment**

A total of 532 patients were enrolled at 28 centers between December 1999 and May 2000; data were collected through July 31, 2001. After central review of data, the diagnosis of chronic-phase CML was confirmed in 454 patients (85 percent). Such a diagnosis could not be confirmed for 17 patients who had characteristics of the accelerated phase of CML, 12 patients who had characteristics of the blast phase (for 11 of whom this diagnosis was based on enlarged lymph nodes only), and 49 patients with missing data.

The characteristics of the patients were typical of patients with interferon-treated, late-chronic-phase CML (Table 1). The median duration of treatment with imatinib was 17.9 months (range, 0.5 to 20.3); 90 percent of the patients were treated for at least 12 months. Of the 532 patients who were enrolled, 87 percent are still receiving imatinib treatment, and 71 patients (13 percent) have discontinued therapy because of disease progression (in 42 patients), adverse events (in 12 patients), abnormal laboratory findings (in 1 patient), protocol violations (in 3 patients), withdrawal of consent (in 7 patients), administrative reasons (in 1 patient), or death (in 5 patients).

**Efficacy**

Of the 454 patients with a confirmed diagnosis of chronic-phase CML, 272 (60 percent) had a major cytogenetic response and 343 (76 percent) had a major, minor, or minimal cytogenetic response. Of the 272 patients with a major cytogenetic response, 188 (69 percent; 41 percent of the total) had a com-

plete response (Table 2). Cytogenetic response rates were highest among patients who had had a cytogenetic relapse while receiving interferon and lowest among patients with hematologic resistance (P=0.001 by the chi-square test). The time to onset of a major cytogenetic response ranged from 2.4 to 19 months.

Of the 272 patients in whom a major cytogenetic response was achieved, 228 (84 percent) continue to have such a response as of last follow-up, whereas the other 44 (16 percent) had a cytogenetic relapse (defined as at least 65 percent Ph-chromosome-positive cells in metaphase or an increase of at least 30 percent from the previous study). The median time to cytogenetic relapse was 12 months (range, 6 to 19) from the start of therapy and 6 months (range, 3 to 14) from the initial achievement of a major cytogenetic response. Of these 44 patients, 5 had progression to an accelerated or blast phase of CML and have discontinued treatment with imatinib. The remaining 39 patients are still receiving the drug. In 15 of these 39 patients, the cytogenetic relapse had reverted to a major cytogenetic response by the time of the karyotypic analysis.

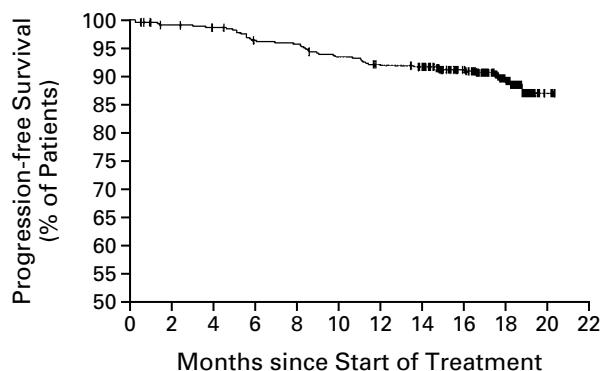
Complete hematologic responses were reported for 430 of the 454 patients studied (95 percent) (Table 2). The median time to a complete hematologic response was 0.7 month; 86 percent of patients who had a response did so within 3 months.

The estimated rate of progression-free survival at 18 months was 89 percent (95 percent confidence interval, 86 to 92 percent), and was similar for the three subgroups of patients (those with hematologic failure, those with cytogenetic failure, and those with intolerance to interferon) (Fig. 1). The achievement of

**TABLE 2. CYTOGENETIC AND HEMATOLOGIC RESPONSES.\***

RESPONSE	ALL PATIENTS WITH CHRONIC-PHASE CML (N=454)	PATIENTS WITH HEMATOLOGIC FAILURE OF INTERFERON TREATMENT		PATIENTS WITH CYTOGENETIC FAILURE OF INTERFERON TREATMENT		PATIENTS WITH INTOLERANCE OF INTERFERON (N=161)
		RESISTANCE (N=63)	RELAPSE (N=70)	RESISTANCE (N=119)	RELAPSE (N=41)	
		number (percent)				
Cytogenetic response						
Major	272 (60)	26 (41)	40 (57)	66 (55)	34 (83)	106 (66)
Complete	188 (41)	16 (25)	29 (41)	37 (31)	31 (76)	75 (47)
Partial	84 (19)	10 (16)	11 (16)	29 (24)	3 (7)	31 (19)
Minor	21 (5)	5 (8)	1 (1)	10 (8)	1 (2)	4 (2)
Minimal	50 (11)	10 (16)	11 (16)	11 (9)	1 (2)	17 (11)
Complete hematologic response	430 (95)	56 (89)	69 (99)	115 (97)	40 (98)	150 (93)

\*The level of cytogenetic response was defined by the percentage of Ph-chromosome-positive cells in metaphase: complete response, 0 percent; partial response, 1 to 35 percent; minor response, 36 to 65 percent; minimal response, 66 to 95 percent; no response, more than 95 percent. A major cytogenetic response was defined as a complete or partial response.



**Figure 1.** Time to Progression to Accelerated Phase or Blast Phase of CML.

Of the 454 patients studied, disease had progressed to the accelerated or blast phase in 47 (10.4 percent) by the time of the analysis. However, only 35 of these 47 patients discontinued medication because of this progression. The estimated rate of progression-free survival was 91.9 percent (95 percent confidence interval, 89.4 to 94.5) at 12 months and 89.2 percent (95 percent confidence interval, 86.2 to 92.3) at 18 months. Tick marks indicate the dates on which data were censored for a given patient.

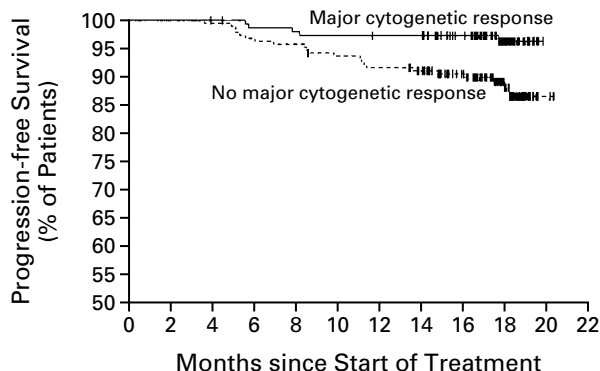
a cytogenetic response at three months was associated with a higher rate of progression-free survival, according to a landmark analysis (Fig. 2).

A total of 149 patients had their dose increased during the study. Among these patients, a hematologic response was achieved in 14 (9 percent) after the dose was increased, and a cytogenetic response was achieved in 17 (11 percent). The estimated survival rate at 18 months for the 454 patients studied was 95 percent and was similar for the three subgroups of patients (data not shown).

**Prognostic Factors**

Associations between base-line variables and the rates of major cytogenetic response are shown in Table 3. Data for two base-line variables (the percentage of Ph-chromosome-positive metaphases and the presence or absence of clonal evolution, defined as the presence of cytogenetic abnormalities other than a variant Ph chromosome, loss of the Y chromosome, or constitutional chromosomal aberrations) were unavailable for several patients. Therefore, we performed two separate multivariate analyses — one excluding these factors (Table 3) and one considering all factors but excluding the patients with missing data.

According to univariate analyses, 14 base-line variables were predictive of higher rates of major cytogenetic response, including response to previous interferon therapy (the presence or absence of hematologic or cytogenetic relapse or resistance). According to the multivariate analyses, the five base-line variables that



**Figure 2.** Landmark Analysis of Time to Progression According to the Cytogenetic Response at Three Months.

All patients remaining in the study at three months were categorized according to the presence or absence of a major cytogenetic response, and these subgroups were analyzed for time to progression (as defined in the Methods section). The analysis included the 343 patients in whom at least 20 cells in metaphase had been cytogenetically analyzed by three months. Of these 343 patients, 152 had a major cytogenetic response (no more than 35 percent Ph-chromosome-positive cells in metaphase). Whereas CML progressed in only 5 of the patients with a major cytogenetic response (3.3 percent), disease progression has been documented in 22 of the 191 patients without such a response (11.5 percent;  $P=0.005$  by the log-rank test). Tick marks indicate the dates on which data were censored for a given patient.

independently predicted a high rate of major cytogenetic response were the absence of blasts in peripheral blood, a hemoglobin level of more than 12 g per deciliter, the presence of less than 5 percent blasts in marrow, a time from diagnosis of CML to start of treatment of less than one year, and a history of cytogenetic relapse during interferon therapy. The inclusion of clonal evolution as a factor did not change the outcome of the multivariate model; the predictive value of the percentage of Ph-chromosome-positive cells in metaphase at the start of treatment was significant ( $P<0.01$ ).

**Efficacy According to the Intention-to-Treat Analysis**

The results with regard to efficacy among all 532 enrolled patients were similar to those among the 454 patients with confirmed chronic-phase CML. The rate of major cytogenetic response in the larger group was 60 percent, and the rate of complete hematologic response was 95 percent. At 18 months, the estimated rate of progression-free survival was 88 percent, and estimated survival was 94 percent. The rates of cytogenetic and hematologic responses were similar among the 17 patients with features of accelerated-phase CML (59 percent and 88 percent, respective-

**TABLE 3.** PROGNOSTIC FACTORS ASSOCIATED WITH A MAJOR CYTOGENETIC RESPONSE ACCORDING TO A MULTIVARIATE ANALYSIS.\*

VARIABLE	NO. OF PATIENTS	PATIENTS WITH A RESPONSE TO IMATINIB MESYLATE no. (%)	P VALUE		ODDS RATIO FOR RESPONSE TO IMATINIB
			UNIVARIATE ANALYSIS	MULTIVARIATE ANALYSIS†	
Response to interferon therapy			<0.001	<0.001	
Hematologic resistance	61	25 (41)			0.35
Hematologic relapse	69	40 (58)			0.96
Cytogenetic resistance	119	66 (55)			0.69
Cytogenetic relapse	41	34 (83)			3.47
Interferon intolerance	160	105 (66)			1.00
Age			0.29		
<60 yr	269	156 (58)			
≥60 yr	181	114 (63)			
Sex			<0.001		
Male	267	175 (66)			
Female	183	95 (52)			
Weight			<0.001		
<70 kg	125	60 (48)			
≥70 kg	325	210 (65)			
Hepatomegaly			0.19		
No	412	251 (61)			
Yes	38	19 (50)			
Splenomegaly			<0.001		
No	370	234 (63)			
Yes	80	36 (45)			
Time since diagnosis of CML			<0.001	<0.001	
<1 yr	37	29 (78)			4.42
1–2 yr	205	139 (68)			2.46
≥3 yr	208	102 (49)			1.00
Hemoglobin			<0.001	<0.001	
<12 g/dl	170	85 (50)			0.49
≥12 g/dl	280	185 (66)			1.00
White-cell count			<0.001		
<10,000/mm <sup>3</sup>	160	116 (72)			
10,000–49,999/mm <sup>3</sup>	208	120 (58)			
≥50,000/mm <sup>3</sup>	82	34 (41)			
Platelet count			<0.001		
<450,000/mm <sup>3</sup>	303	202 (67)			
450,000–699,999/mm <sup>3</sup>	82	45 (55)			
≥700,000/mm <sup>3</sup>	65	23 (35)			
Basophils			0.10		
<7%	392	241 (61)			
≥7%	58	29 (50)			
Blasts in peripheral blood			<0.001	<0.001	
0%	328	222 (68)			2.52
0–2%	83	35 (42)			1.04
≥3%	39	13 (33)			1.00
Blasts in bone marrow			0.01	0.01	
<5%	376	239 (64)			2.06
≥5%	74	31 (42)			1.00
Ph-chromosome–positive cells in metaphase			<0.001		
<90%	55	49 (89)			
≥90%	378	211 (56)			
Clonal evolution‡			0.18		
No	379	233 (61)			
Yes	54	28 (52)			

\*The analysis included the 450 patients who could be evaluated for cytogenetic response and had data available on all base-line factors. Odds ratios are for the comparisons with the reference category (odds ratio, 1.00) for each variable that was significant at  $P < 0.1$  in the multivariate regression model. Data on Philadelphia-chromosome–positive cells in metaphase and clonal evolution were missing for 17 patients.

†P values are given only for variables that remained significant in the multivariate regression model.

‡Clonal evolution was defined as the presence of cytogenetic abnormalities other than a variant Ph chromosome, loss of the Y chromosome, or constitutional chromosomal aberrations.

ly) and the 12 with features of blastic-phase CML (75 percent and 92 percent, respectively).

**Safety**

Common adverse events included superficial edema, nausea, and muscle cramps (Table 4). Grade 3 or 4 events were infrequent; the most common grade 3 or 4 event was weight gain. Grade 3 or 4 neutropenia was noted during the study in 35 percent of the patients, and thrombocytopenia was found in 20 percent of the patients (Table 4). The median time to a first grade 3 or 4 episode of neutropenia was 62 days (range, 8 to 463); the median time to a first grade 3 or 4 episode of thrombocytopenia was 57 days (range, 8 to 581). The median duration of thrombocytopenia was 18 days, and the median duration of neutropenia was 21 days.

Drug-related adverse events — including thrombocytopenia, nausea, vomiting, fever, hepatic toxic effects, arthralgia, hemorrhagic stroke, exanthem, and rash — led to the discontinuation of therapy in 11 patients (2.1 percent). Serious drug-related adverse events were reported in 29 patients (5.5 percent); these events included rash (in 4 patients), febrile neutropenia (in 4 patients), hepatic toxic effects (in 4 patients), neutropenia, thrombocytopenia, nausea, vomiting, fever, and fluid retention and diarrhea (in 2 patients each). Five patients died during therapy — one from myocardial infarction attributed to preexisting cardiovascular disease, one from a cerebrovascular accident, one from progressive CML, one from subarachnoid hemorrhage, and one from cerebral hemorrhage. Eight patients died within 28 days after the discontinuation of therapy for progressive disease — five from progressive CML, one from sepsis, one from cardiogenic shock, and one from pulmonary embolism.

**DISCUSSION**

In this phase 2 study of imatinib mesylate in patients with chronic-phase CML in whom treatment with interferon had failed, the rates of major and complete cytogenetic responses were 60 percent and 41 percent, respectively. Treatment was well tolerated; serious drug-related adverse events occurred in less than 6 percent of patients, and hematologic toxic effects were manageable.

The rates of major and complete cytogenetic responses we observed were higher than those reported in patients treated with interferon (15 percent and 5 to 7 percent, respectively) or homoharringtonine, a plant alkaloid, either alone<sup>23</sup> or in combination with low-dose cytarabine.<sup>24</sup> The estimated 18-month progression-free survival rate of 89 percent is also higher than in trials of interferon or homoharringtonine.<sup>23-25</sup> Our results cannot be attributed to a bias

**TABLE 4. ADVERSE EVENTS RELATED TO TREATMENT WITH IMATINIB MESYLATE.\***

EVENT	NO. OF PATIENTS WITH EVENT (%)	
	ANY GRADE	GRADE 3 OR 4
<b>Nonhematologic</b>		
Superficial edema	318 (60)	6 (1.1)
Nausea	293 (55)	8 (1.5)
Muscle cramps	261 (49)	5 (0.9)
Rash and related events	171 (32)	16 (3.0)
Diarrhea	152 (29)	5 (0.9)
Weight gain	137 (26)	23 (4.3)
Vomiting	125 (23)	3 (0.6)
Myalgia	108 (20)	1 (0.2)
Arthralgia	100 (19)	4 (0.8)
Abdominal pain	99 (19)	0
Fatigue	95 (18)	2 (0.4)
Dyspepsia	93 (17)	0
Musculoskeletal pain	71 (13)	3 (0.6)
Headache	69 (13)	0
Pruritus	46 (9)	2 (0.4)
		GRADE 3    GRADE 4
<b>Hematologic</b>		
Anemia		30 (6)    6 (1.1)
Thrombocytopenia		101 (19)    5 (0.9)
Leukopenia		115 (22)    9 (1.7)
Neutropenia		143 (27)    43 (8.1)

\*Adverse events include conditions that worsened from base line or developed during treatment in more than 5 percent of the patients. All 532 enrolled patients were included in the analysis. Hematologic events were graded as follows, according to the Common Toxicity Criteria of the National Cancer Institute: grade 3 was defined by a neutrophil count of 500 to 999 per cubic millimeter, a platelet count of 10,000 to 49,999 per cubic millimeter, a hemoglobin level of 6.5 to 8.0 g per deciliter, or a leukocyte count of 1000 to 1999 per cubic millimeter; grade 4 was defined by a neutrophil count of less than 500 per cubic millimeter, a platelet count of less than 10,000 per cubic millimeter, a hemoglobin level of less than 6.5 g per deciliter, or a leukocyte count of less than 1000 per cubic millimeter.

in favor of patients with a favorable prognosis, since the factors associated with a poor prognosis in this trial were similar to those in other studies of patients with CML in the late chronic phase.<sup>23,25</sup> In these published series, the failure of interferon therapy was also predictive of a poor subsequent outcome, with an annual mortality rate of 10 to 20 percent.

In our study, factors associated with a high rate of major cytogenetic response were similar to those identified in previous studies and tend to be associated with less advanced disease or a history of hematologic or cytogenetic responsiveness to treatment with interferon. Anemia, low platelet counts, and high blast counts in peripheral blood or marrow correlated with a poor outcome in this study, as well as in other studies of imatinib in advanced phases of CML.<sup>22</sup> Longer follow-up of the patients enrolled in this trial should allow the identification of factors associated with the progression of disease as well as those associated with longer survival.

Because imatinib is well tolerated, it may be feasible to combine it with other agents to treat interferon-resistant CML in the late chronic phase or to optimize the status of the disease before performing allogeneic stem-cell transplantation. In this study, disease progression occurred in nearly 10 percent of patients within 18 months. Regimens that combine imatinib with other agents may improve results further, and ongoing clinical trials are testing the feasibility of these approaches. The activity of imatinib is also being investigated in patients with newly diagnosed CML in a randomized phase 3 study comparing imatinib with standard interferon plus low-dose cytarabine.<sup>26</sup>

*Note added in proof:* Updated follow-up data were available for 149 patients as of February 1, 2002 (median follow-up, 26 months). Among these patients, the overall rate of major cytogenetic response was 64 percent, and the rate of complete cytogenetic response was 49 percent. The estimated rate of progression-free survival at 24 months was 87 percent, and the estimated 24-month survival rate was 92 percent. A total of 13 of the 149 patients (9 percent) have died, 9 from progressive disease and 4 from other causes.

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## APPENDIX

In addition to the authors, the following investigators participated in the International STI571 CML Study: United Kingdom — J. Goldman (Hammer-smith Hospital, Imperial College School of Medicine, London), S.G. O'Brien (Royal Victoria Infirmary, University of Newcastle upon Tyne, Newcastle upon Tyne), N. Russell (City Hospital, Nottingham); Germany — T. Fischer (Johannes Gutenberg-Universität, Mainz), O. Ottmann (Johann Wolfgang Goethe-Universität, Frankfurt); France — P. Cony-Makhoul (Laboratoire de Greffe de Moelle, Université Victor Segalen, Bordeaux), T. Facon (Hôpital Claude Huriez, Centre Hospitalier Régional Universitaire de Lille, Lille); United States — R. Stone (Dana Farber Cancer Institute, Boston), C. Miller (Johns Hopkins Oncology Center, Baltimore), M. Tallman (Northwestern University Medical School, Chicago), R. Brown (Washington University School of Medicine, St. Louis), M. Schuster (New York Presbyterian Hospital–Weill Medical College of Cornell University, New York), T. Loughran (University of South Florida, Tampa, Fla.); Switzerland — A. Gratwohl (Universitätsklinik, Kantonsspital, Basel); Italy — F. Mandelli (Università La Sapienza, Rome), G. Saglio (Università di Torino, Orbassano), M. Lazzarino (Istituto di Ricovero e Cura a Carattere Scientifico Policlinico S. Matteo, Pavia), D. Russo (Udine University Hospital, Udine), M. Baccarani (Università di Bologna, Bologna), E. Morra (Azienda Ospedaliera Niguarda Ca'Granda, Milan). All statistical analyses were performed by U. Zoellner and I. Gathmann.

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**CORRECTION**

**Hematologic and Cytogenetic Responses to Imatinib Mesylate in Chronic Myelogenous Leukemia**

Hematologic and Cytogenetic Responses to Imatinib Mesylate in Chronic Myelogenous Leukemia . The following persons should have been listed as authors: John Goldman (Hammersmith Hospital, Imperial College School of Medicine, London), Stephen G. O'Brien (Royal Victoria Infirmary, University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom), Nigel Russell (City Hospital, Nottingham, United Kingdom), Thomas Fischer (Johannes Gutenberg Universität, Mainz, Germany), Oliver Ottmann (Johann Wolfgang Goethe-Universität, Frankfurt, Germany), Pascale Cony-Makhoul (Université Victor Segalen, Bordeaux, France), Thierry Facon (Hôpital Claude Huriez, Centre Hospitalier Régional Universitaire de Lille, Lille, France), Richard Stone (Dana-Farber Cancer Institute, Boston), Carole Miller (Johns Hopkins Oncology Center, Baltimore), Martin Tallman (Northwestern University Medical School, Chicago), Randy Brown (Washington University School of Medicine, St. Louis), Michael Schuster (New York Presbyterian Hospital-Weill Medical College of Cornell University, New York), Thomas Loughran (University of South Florida, Tampa), Alois Gratwohl (Kantonsspital, Basel, Switzerland), Franco Mandelli (Università La Sapienza, Rome), Giuseppe Saglio (Università di Torino, Orbassano, Italy), Mario Lazarino (Istituto di Ricovero e Cura a Carattere Scientifico Policlinico S. Matteo, Pavia, Italy), Domenico Russo (Udine University Hospital, Udine, Italy), Michele Baccarani (Università di Bologna, Bologna, Italy), and Enrica Morra (Azienda Ospedaliera Niguarda Ca'Granda, Milan, Italy).