

ORIGINAL ARTICLE

Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia

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ABSTRACT

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*Other participants in the International Randomized Study of Interferon and ST1571 (IRIS) trial are listed in the Appendix.

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BACKGROUND

Imatinib, a selective inhibitor of the BCR-ABL tyrosine kinase, produces high response rates in patients with chronic-phase chronic myeloid leukemia (CML) who have had no response to interferon alfa. We compared the efficacy of imatinib with that of interferon alfa combined with low-dose cytarabine in newly diagnosed chronic-phase CML.

METHODS

We randomly assigned 1106 patients to receive imatinib (553 patients) or interferon alfa plus low-dose cytarabine (553 patients). Crossover to the alternative group was allowed if stringent criteria defining treatment failure or intolerance were met. Patients were evaluated for hematologic and cytogenetic responses, toxic effects, and rates of progression.

RESULTS

After a median follow-up of 19 months, the estimated rate of a major cytogenetic response (0 to 35 percent of cells in metaphase positive for the Philadelphia chromosome) at 18 months was 87.1 percent (95 percent confidence interval, 84.1 to 90.0) in the imatinib group and 34.7 percent (95 percent confidence interval, 29.3 to 40.0) in the group given interferon alfa plus cytarabine ($P < 0.001$). The estimated rates of complete cytogenetic response were 76.2 percent (95 percent confidence interval, 72.5 to 79.9) and 14.5 percent (95 percent confidence interval, 10.5 to 18.5), respectively ($P < 0.001$). At 18 months, the estimated rate of freedom from progression to accelerated-phase or blast-crisis CML was 96.7 percent in the imatinib group and 91.5 percent in the combination-therapy group ($P < 0.001$). Imatinib was better tolerated than combination therapy.

CONCLUSIONS

In terms of hematologic and cytogenetic responses, tolerability, and the likelihood of progression to accelerated-phase or blast-crisis CML, imatinib was superior to interferon alfa plus low-dose cytarabine as first-line therapy in newly diagnosed chronic-phase CML.

THE PHILADELPHIA CHROMOSOME (Ph),¹ the result of a t(9;22) reciprocal translocation,² is present in over 90 percent of patients with chronic myeloid leukemia (CML) and results in the juxtaposition of DNA sequences from the BCR and ABL genes.³⁻⁶ BCR-ABL encodes a protein, p210^{BCR-ABL}, with dysregulated tyrosine kinase activity,⁷ which is necessary and sufficient for leukemogenesis.⁸⁻¹¹ Imatinib mesylate (Gleevec, Novartis), a potent competitive inhibitor of the tyrosine kinases associated with ABL,^{12,13} C-KIT,^{14,15} platelet-derived growth factor receptor,^{13,14,16} and ARG,¹⁷ impedes the interaction of ATP with these proteins¹⁸ and thereby inhibits their ability to phosphorylate and activate proteins downstream.

After an initial phase 1 dose-escalation study of imatinib in patients with CML,¹⁹ a phase 2 study involving 532 patients with late chronic-phase CML who had had an unsatisfactory response to interferon alfa was conducted that used a dose of 400 mg of oral imatinib once daily. Imatinib was well tolerated, and 60 percent of the patients had a major cytogenetic response (defined by the finding that no more than 35 percent of cells in metaphase were Ph-positive); 41 percent had a complete cytogenetic response.²⁰ After a median follow-up of 18 months, 95 percent of patients were alive and the disease was still in the chronic phase in 89 percent.

Although allogeneic hematopoietic-cell transplantation is the only proven curative treatment for CML, the procedure is an option in only about 25 percent of patients and carries substantial risks.²¹⁻²³ In prospective, randomized studies, interferon alfa has produced rates of major cytogenetic responses of 11 to 30 percent and complete cytogenetic responses in about 10 percent of patients.²⁴ Most,²⁵⁻²⁸ although not all,²⁹ of these studies have demonstrated a survival advantage with interferon alfa, as compared with hydroxyurea (or busulfan), although interferon alfa is not considered curative. An overview of seven such studies indicated an absolute overall improvement in five-year survival rates with interferon alfa treatment of 15 percent (from 42 to 57 percent), as compared with either hydroxyurea or busulfan treatment.²⁴

In the present prospective, multicenter, open-label, phase 3, randomized study (the IRIS [International Randomized Study of Interferon and STI571] trial), the combination of recombinant interferon alfa and low-dose cytarabine was adopted as the standard for comparison with imatinib, since this

combination results in superior rates of cytogenetic response and survival as compared with interferon alfa alone.³⁰ However, interferon alfa plus low-dose cytarabine requires regular subcutaneous injections of two drugs, and side effects are frequent and troublesome. A recent comparison of interferon alfa with interferon alfa plus cytarabine confirmed that superior rates of cytogenetic response can be achieved with the combination but did not demonstrate a significant difference in survival.³¹

METHODS

PATIENTS

Patients were eligible for the study if they were between 18 and 70 years of age and had received a diagnosis of chronic-phase, Ph-positive CML within six months before study entry. 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. Patients were excluded if they had extramedullary disease other than hepatosplenomegaly or fewer than 100,000 platelets per cubic millimeter unrelated to therapy. The presence of other cytogenetic abnormalities in addition to Ph did not exclude patients from the study. Patients had to have been previously untreated for CML, with the exception of hydroxyurea, anagrelide, or both. Levels of liver aminotransferases, serum bilirubin, and serum creatinine that were no higher than 1.5 times the upper limit of the normal range were required. Women who were breast-feeding, pregnant, or of childbearing potential without a negative pregnancy test were not enrolled. Patients were excluded if their Eastern Cooperative Oncology Group performance status was 3 or higher (poor), they had other uncontrolled serious medical conditions, they had received prior chemotherapy or treatment with any investigational agent, they had undergone hematopoietic-cell transplantation, they had undergone major surgery within the preceding four weeks, they were known to be seropositive for the human immunodeficiency virus (screening was not required), or they had a history of another cancer within the previous five years, with the exception of basal-cell carcinoma or cervical carcinoma in situ. The prognostic scores of Sokal et al.³² and Hasford et al.³³ were determined; these scores were not available for some patients who were referred from outside centers.

Individual investigators used a computerized telephone system for randomization, and no block-

ing was used. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was reviewed by the ethics committees or institutional review boards of all participating centers. All patients gave written informed consent according to institutional regulations.

STUDY DESIGN AND TREATMENTS

This prospective, multicenter, open-label, phase 3, randomized, controlled trial was conducted in an outpatient setting. Patients in the imatinib group received 400 mg orally daily. Patients assigned to interferon alfa plus cytarabine (combination therapy) received gradually escalating doses of interferon alfa (target dose, 5 million U per square meter of body-surface area per day) as long as grade 3 (severe) or grade 4 (life-threatening) toxicity did not occur. Once the maximal tolerated dose of interferon alfa was achieved, subcutaneous low-dose cytarabine was added at a dose of 20 mg per square meter per day (maximal daily dose, 40 mg) for 10 days every month. The concurrent administration of hydroxyurea in either treatment group was permitted during the first six months of treatment to keep the white-cell count below 20,000 per cubic millimeter. Treatment in both groups was continued until the patient no longer derived benefit from the medication.

The study was designed by the investigators and representatives of the sponsor, Novartis. The data were collected with use of the data-management and statistical-support systems of Novartis and analyzed and interpreted by a statistician from Novartis in close collaboration with the investigators. The study-management committee (see the Appendix), which was also the writing committee, and all academic investigators had access to the raw data. An independent data-monitoring board (see the Appendix) reviewed the trial data on two occasions and made recommendations regarding the timing of disclosure of the data that were based on safety, tolerability, and efficacy.

END POINTS

The primary end point was progression, which was defined by any of the following events, whichever came first: death from any cause during treatment, the development of accelerated-phase CML (defined by the presence of at least 15 percent blasts in the blood or bone marrow, at least 30 percent blasts plus promyelocytes in the blood or bone marrow, at least 20 percent peripheral basophils, or throm-

bocytopenia [fewer than 100,000 platelets per cubic millimeter] unrelated to treatment) or blast-phase CML (defined by the presence of at least 30 percent blasts in the blood or bone marrow or extramedullary involvement [e.g., chloromas], but not hepatosplenomegaly), loss of complete hematologic response (defined by the appearance of any of the following in two blood samples obtained at least one month apart: a white-cell count of more than 20,000 per cubic millimeter, a platelet count of at least 600,000 per cubic millimeter, the appearance of extramedullary disease, the appearance of at least 5 percent myelocytes and metamyelocytes in the peripheral blood, or the appearance of blasts or promyelocytes in the peripheral blood), loss of major cytogenetic response (defined as an increase in Ph-positive cells in metaphase by at least 30 percentage points on two cytogenetic analyses performed at least one month apart), or an increasing white-cell count (defined as a doubling of the count to more than 20,000 per cubic millimeter on two occasions at least one month apart in a patient who had never strictly had a complete hematologic response despite receiving maximally tolerated doses of therapy).

Secondary end points were the rate of complete hematologic response (as 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 plus metamyelocytes, the presence of less than 20 percent basophils and the absence of blasts and promyelocytes in peripheral blood, and the absence of extramedullary involvement), the rate of major cytogenetic response (categorized as either complete [0 percent Ph-positive cells in metaphase in a bone marrow sample] or partial [1 to 35 percent Ph-positive cells in metaphase], as determined on the basis of G-banding in at least 20 cells in metaphase per sample), safety, and tolerability.

DOSE MODIFICATIONS

For patients in the imatinib group who did not have a complete hematologic response at 3 months or at least a minor cytogenetic response (defined by the finding of 36 to 65 percent Ph-positive cells in metaphase) at 12 months, the dose could be escalated to 400 mg twice daily in the absence of dose-limiting adverse effects. For patients in the combination-therapy group who were receiving the maximal tolerated dose of interferon alfa, the dose of cytarabine could be increased up to 40 mg per

day for 15 days each month if a complete hematologic response at 3 months or at least a minor cytogenetic response at 12 months was not achieved.

CROSSOVERS

All crossover requests were stripped of identifiers and evaluated weekly by the study-management committee. Patients were allowed to cross over to the other group if they had no response, had a loss of response, had an increase in the white-cell count, or could not tolerate treatment (a situation defined by the recurrence of nonhematologic toxicity of at least grade 3 despite appropriate dose reductions and optimal symptomatic management); crossover was allowed for any patient who had an adverse effect that was considered immediately life-threatening.

STATISTICAL ANALYSIS

The sample-size calculation was based on projected differences in progression rates. The aim was to detect a relative hazard ratio of 0.75 for the imatinib group relative to the combination-therapy group, given an estimated five-year rate of progression-free survival of 50 percent for the combination-therapy group and approximately 60 percent for the imatinib group. With a planned median follow-up of 5.25 years and an enrollment period of 0.5 year, 822 patients needed to undergo randomization to yield the required 385 events (with use of a two-tailed log-rank test at the 5 percent level of significance and a statistical power of 80 percent). To allow for a yearly dropout rate of 10 percent, the recruitment target was 1032 patients. The analysis of the primary end point was performed on an intention-to-treat basis regardless of whether crossover occurred; all other variables were analyzed only for the initial treatment period (until patients crossed over or discontinued treatment).

The 95 percent confidence intervals for observed response rates were calculated with the use of Pearson-Clopper limits, and the difference in treatments was evaluated with Fisher's exact test. Rates of hematologic and cytogenetic response were estimated according to the Kaplan-Meier method,³⁴ in which data on patients who crossed over to the alternative treatment group or discontinued treatment for reasons other than progression were censored at the last follow-up visit of the initial treatment period. The treatment effect was evaluated with the log-rank test.

Safety was analyzed for all patients who received at least one dose of study drug: 551 in the imatinib

Table 1. Base-Line Characteristics of the Patients.*

Characteristic	Imatinib (N=553)	Interferon Alfa plus Cytarabine (N=553)
Age		
Median — yr	50	51
Range — yr	18–70	18–70
≥60 yr — no. (%)	114 (20.6)	128 (23.1)
Sex — no. (%)		
Male	341 (61.7)	310 (56.1)
Female	212 (38.3)	243 (43.9)
ECOG performance status — no. (%)		
0	425 (76.9)	409 (74.0)
1	115 (20.8)	121 (21.9)
2	8 (1.4)	11 (2.0)
Data missing	5 (0.9)	12 (2.2)
Interval since diagnosis — mo		
Median	2.1	1.8
Range	0.0–10.4	0.0–8.0
Sokal risk group — no. (%)		
Total evaluated	383 (69.3)	394 (71.2)
Low	201 (52.5)	190 (48.2)
Intermediate	111 (29.0)	117 (29.7)
High	71 (18.5)	87 (22.1)
Hasford risk group — no. (%)		
Total evaluated	375 (67.8)	388 (70.2)
Low	171 (45.6)	173 (44.6)
Intermediate	166 (44.3)	176 (45.4)
High	38 (10.1)	39 (10.1)
Chromosomal abnormalities in addition to the Philadelphia chromosome — no. (%)		
No	456 (82.5)	488 (88.2)
Yes	67 (12.1)	42 (7.6)
Trisomy 8	4 (0.7)	4 (0.7)
Isochromosome 17	1 (0.2)	1 (0.2)
Trisomy 19	1 (0.2)	1 (0.2)
Double Philadelphia chromosome	3 (0.5)	0
Trisomy 21	0	1 (0.2)
Loss of sex chromosome	10 (1.8)	11 (2.0)
Other	50 (9.0)	30 (5.4)
Data missing	30 (5.4)	23 (4.2)
Splenomegaly — no. (%)	127 (23.0)	150 (27.1)
Spleen size ≥10 cm below costal margin — no. (%)	33 (6.0)	33 (6.0)
White-cell count — ×10 ⁻³ /mm ³		
Median	17.9	20.2
Range	1.6–421.3	2.0–500.0
Platelet count — ×10 ⁻³ /mm ³		
Median	336	340
Range	47–2950	18–3412
Hemoglobin — g/dl		
Median	13.0	12.8
Range	6.9–17.5	6.6–19.4
Peripheral-blood blasts — %		
Median	0.0	0.0
Range	0.0–14.0	0.0–14.0
Peripheral-blood basophils — %		
Median	3.0	3.0
Range	0.0–39.0	0.0–26.0

* Values for the calculation of the Sokal and Hasford scores were unavailable for 329 (29.7 percent) patients and 343 (31.0 percent) patients, respectively. ECOG denotes Eastern Cooperative Oncology Group.

Table 2. Patients' Treatment Status as of July 31, 2002.*

Variable	Imatinib (N=553)	Interferon Alfa plus Cytarabine (N=553)
	No. of Patients (%)	
Continued initial treatment	474 (85.7)	60 (10.8)
Discontinued initial treatment	68 (12.3)	175 (31.6)
Adverse events	12	33
Disease progression	18	29
Proceeded to allograft transplantation	8	7
Protocol violation	10	17
Withdrew consent	12	75
Lost to follow-up	2	6
Administrative problems	0	6
Died	6	2
Crossed over to alternative treatment	11 (2.0)	318 (57.5)
Disease progression		
Increase in white-cell count	2	25
Loss of complete hematologic response	3	28
Loss of major cytogenetic response	1	10
Reason other than disease progression		
Intolerance of treatment	4	136
No complete hematologic response at 6 mo	0	41
No complete hematologic response or major cytogenetic response at 12 mo†	1	53
Reluctance to continue interferon alfa plus cytarabine†	0	25
Continued alternative treatment	6	284
Discontinued alternative treatment	5	34

* Discontinuation and crossover are mutually exclusive groups. Crossover because of an increase in the white-cell count or intolerance of treatment required the approval of the study-management committee.

† This reason for crossover was introduced 12 months after the last patient was recruited, on the basis of a recommendation by the independent data-monitoring board.

group and 533 in the combination-therapy group. Efficacy was analyzed in the intention-to-treat population — that is, all 553 patients who were randomly assigned to the imatinib group and all 553 who were assigned to combination therapy.

RESULTS

PATIENTS AND TREATMENTS

The study was conducted in 177 hospitals in 16 countries, and 1106 patients (553 in each group) were enrolled between June 2000 and January 2001.

The data as of January 31, 2002, were then submitted to the health authorities of countries participating in the study as part of the approval process for the use of imatinib in newly diagnosed chronic-phase CML. The current analysis is based on data collected up to July 31, 2002. The median follow-up was 19 months. The only significant difference in base-line characteristics between the two groups was that more patients in the imatinib group than in the combination-therapy group had chromosomal abnormalities in addition to Ph (12.1 percent vs. 7.6 percent, $P=0.015$). Risk stratification on the basis of the prognostic scores of Sokal et al.³² and Hasford et al.³³ produced similar results in the two groups (Table 1). The median dose delivered in the imatinib group was 400 mg daily (range, 114 to 732). In the combination-therapy group, the median delivered dose of interferon alfa was 4.8 million U per day (range, 0.6 million to 11.3 million); 159 patients (28.8 percent) never received cytarabine, but among the 394 (71.2 percent) who did, the median number of courses was 4 (range, 1 to 23). Hydroxyurea was given to 45 percent of the patients in the imatinib group (median, 15 days) and 75 percent of patients in the combination-therapy group (median, 30 days).

CROSSOVER, DISCONTINUATION, SAFETY, AND TOLERABILITY

A total of 79 patients (14.3 percent) in the imatinib group and 493 patients (89.2 percent) in the combination-therapy group either discontinued treatment or crossed over to the alternative treatment group (Table 2). Discontinuations and crossovers were mutually exclusive groups. In the combination-therapy group, the most common reason for crossover was intolerance (136 of 318 patients who crossed over), and for discontinuation, it was withdrawal of consent (75 of 175 patients who discontinued therapy). Most patients who discontinued after withdrawing consent were in the combination-therapy group and did so when the Food and Drug Administration approved imatinib (in May 2001), presumably to receive imatinib therapy outside the confines of the study. A total of 52 patients proceeded to bone marrow transplantation a median of 13 months (range, 5 to 22) after randomization: 18 in the imatinib group (1 of whom had crossed over to the combination-therapy group) and 34 in the combination-therapy group (13 of whom had crossed over to the imatinib group).

The toxicity profiles of the two groups are consistent with published experience (Table 3). Ad-

Table 3. Adverse Events.*

Adverse Event	All Grades		Grade 3 or 4		Adverse Event	All Grades		Grade 3 or 4	
	Imatinib (N=551)	Interferon Alfa plus Cytarabine (N=533)	Imatinib (N=551)	Interferon Alfa plus Cytarabine (N=533)		Imatinib (N=551)	Interferon Alfa plus Cytarabine (N=533)	Imatinib (N=551)	Interferon Alfa plus Cytarabine (N=533)
	<i>percent</i>					<i>percent</i>			
Nonhematologic					Nonhematologic				
Superficial edema	55.5	9.2	0.9	0.6	Anxiety	7.3	11.4	0.2	2.6
Nausea	43.7	61.4	0.7	5.1	Dyspnea	7.3	14.3	1.5	1.5
Muscle cramps	38.3	11.1	1.3	0.2	Pruritus	7.3	11.6	0.2	0.2
Musculoskeletal pain	36.5	42.0	2.7	8.3	Rigors	7.3	33.8	0	0.8
Rash	33.9	25.0	2.0	2.3	Influenza-like illness	7.1	18.6	0	1.1
Fatigue	34.5	65.5	1.1	24.4	Night sweats	7.1	15.6	0.2	0.4
Diarrhea	32.8	41.7	1.8	3.2	Asthenia	5.6	18.6	0.2	3.9
Headache	31.2	42.6	0.4	3.2	Anorexia	5.3	31.7	0	2.4
Joint pain	28.3	39.6	2.4	7.3	Alopecia	4.4	22.3	0	0.6
Abdominal pain	27.0	24.6	2.4	3.9	Increased sweating	3.6	14.8	0	0.4
Nasopharyngitis	22.0	8.3	0	0.2	Weight loss	3.1	17.1	0.2	1.3
Myalgia	21.4	38.8	1.5	8.1	Stomatitis	2.9	12.0	0	0.2
Hemorrhage	20.9	20.6	0.7	1.5	Dry mouth	2.2	10.3	0	0.2
Vomiting	16.9	27.4	1.5	3.4	Mucosal inflammation	0.7	10.3	0	3.2
Dyspepsia	16.2	9.2	0	0.8	Hematologic				
Pharyngolaryngeal pain	16.0	13.3	0.2	0.2	Anemia	44.6	54.8	3.1	4.3
Cough	14.5	22.3	0.2	0.6	Neutropenia	60.8	67.2	14.3	25.0
Dizziness	14.5	23.8	0.9	3.4	Thrombocytopenia	56.6	78.6	7.8	16.5
Upper respiratory tract infection	14.5	8.3	0.2	0.4	Biochemical				
Weight gain	13.4	1.7	0.9	0.2	Elevated serum alanine or aspartate aminotransferase	43.2	73.5	5.1	6.8
Pyrexia	13.1	39.2	0.7	2.8					
Insomnia	12.2	18.8	0	2.3					
Depression	10.2	35.5	0.4	12.8					
Constipation	8.5	14.3	0.7	0.2					

* Adverse events include conditions that worsened from base line or developed during initial treatment in more than 10 percent of the patients and were graded according to the Common Toxicity Criteria of the National Cancer Institute. Hematologic events were graded as follows: grade 3 was defined by a neutrophil count of 500 to less than 1000 per cubic millimeter, a platelet count of 10,000 to less than 50,000 per cubic millimeter, a hemoglobin level of 6.5 to less than 8.0 g per deciliter, or a leukocyte count of 1000 to less than 2000 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. Elevated liver-enzyme levels were considered to be grade 3 if they were 6 to 20 times the upper limit of the normal range and grade 4 if they were more than 20 times the upper limit of the normal range. Data on safety were not available for 2 patients in the imatinib group and 20 patients in the group given interferon alfa plus cytarabine.

verse events in the imatinib group were generally grade 1 (mild) or 2 (moderate), and among the most common were superficial edema, nausea, muscle cramps, and rashes. There were only rare occurrences of grade 3 or 4 events, but such events were much more common in the combination-therapy group and were consistent with the high rate of crossover resulting from intolerance in this group. These adverse events included fatigue, depression, myalgias, arthralgias, neutropenia, and thrombocytopenia. At the time of the analysis, 48 patients in the study had died. Eight patients died during treatment (Table 2) from causes not related to their leukemia, four had cardiac events, one died in a car accident, one died of pneumococcal sepsis, one of pulmonary edema, and one from liver metastasis. A total of 14 patients in the imatinib group and 26 patients in the combination-therapy group died after discontinuing therapy (3 and 5, respectively, after bone marrow transplantation).

RATES OF HEMATOLOGIC AND CYTOGENETIC RESPONSES

Rates of hematologic and cytogenetic responses are shown in Table 4. As well as a higher overall rate of complete hematologic response in the imatinib group than in the combination-therapy group (95.3 percent vs. 55.5 percent, $P < 0.001$), the responses were more rapid. The median interval to a complete hematologic response was 1 month in the imatinib group, as compared with 2.5 months in the combination-therapy group. The estimated rates of complete hematologic response at 18 months were 96.8

percent in the imatinib group and 69.0 percent in the combination-therapy group.

The rate of a major cytogenetic response was 85.2 percent in the imatinib group, as compared with 22.1 percent in the combination-therapy group ($P < 0.001$). In the imatinib group, even among those at high risk according to the Sokal and Hasford scores, the rates of major cytogenetic response were 69.0 percent and 78.9 percent, respectively (complete cytogenetic response, 56.3 percent and 65.8 percent). Using the Kaplan–Meier method, which compensates for the high rates of crossover and discontinuation, particularly in the combination-therapy group, we estimated that the rate of major cytogenetic response at 18 months was 87.1 percent (95 percent confidence interval, 84.1 to 90.0) in the imatinib group and 34.7 percent (95 percent confidence interval, 29.3 to 40.0) in the combination-therapy group ($P < 0.001$) (Fig. 1). The corresponding rates of complete cytogenetic response at 18 months were 76.2 percent (95 percent confidence interval, 72.5 to 79.9) and 14.5 percent (95 percent confidence interval, 10.5 to 18.5; $P < 0.001$).

Of the 318 patients who crossed over to imatinib therapy, 82.4 percent had a complete hematologic response and 55.7 percent had a major cytogenetic response, including 39.6 percent who had a complete cytogenetic response (Table 4). Three of the 11 patients who crossed over from imatinib to combination therapy had a complete hematologic response, but none had a cytogenetic response (Table 4).

Table 4. Rates of Best Observed Hematologic and Cytogenetic Responses.*

Response	Initial Treatment		Crossover Treatment	
	Imatinib (N=553)	Interferon Alfa plus Cytarabine (N=553)	From Imatinib to Interferon Alfa plus Cytarabine (N=11)	From Interferon Alfa plus Cytarabine to Imatinib (N=318)
	<i>percent (95% CI)</i>			
Complete hematologic	95.3 (93.2–96.9)	55.5 (51.3–59.7)†	27.3 (6.0–61.0)	82.4 (77.7–86.4)
Major cytogenetic	85.2 (81.9–88.0)	22.1 (18.7–25.8)†	0 (0–28.5)	55.7 (50.0–61.2)
Complete cytogenetic	73.8 (69.9–77.4)	8.5 (6.3–11.1)†	0 (0–28.5)	39.6 (34.2–45.2)
Partial cytogenetic	11.4 (8.9–14.3)	13.6 (10.8–16.7)	0 (0–28.5)	16.0 (12.2–20.5)

* The level of cytogenetic response was defined by the percentage of Philadelphia-chromosome–positive cells in metaphase: complete response, 0 percent; partial response, 1 to 35 percent. A major cytogenetic response was defined as a complete or partial response. CI denotes confidence interval.

† $P < 0.001$ for the comparison with the imatinib group.

DISEASE PROGRESSION AND SURVIVAL

At 12 months, the disease had not progressed in an estimated 96.6 percent of patients in the imatinib group and 79.9 percent of patients in the combination-therapy group ($P < 0.001$) (Fig. 2A); the respective values at 18 months were 92.1 percent and 73.5 percent. At 12 months, estimated rates of freedom from progression to accelerated-phase or blast-crisis CML were 98.5 percent in the imatinib group and 93.1 percent in the combination-therapy group ($P < 0.001$) (Fig. 2B). The respective values at 18 months were 96.7 percent and 91.5 percent. In all Sokal risk groups, imatinib was significantly superior to combination therapy ($P < 0.001$) (Fig. 2C). The estimated survival rates at 18 months were 97.2 percent for the imatinib group and 95.1 percent for the combination-therapy group ($P = 0.16$). If survival was censored at the time of bone marrow transplantation, the estimated survival rates at 18 months were 97.4 percent for the imatinib group and 95.8 percent for the combination-therapy group ($P = 0.23$).

DISCUSSION

In this randomized study, we compared imatinib with standard therapy for newly diagnosed, chronic-phase CML. On the basis of the marked differences between the two groups, particularly with respect to the rates of progression, the independent data-monitoring board recommended that the data be disclosed. According to all variables measured, including the rates of complete hematologic response, major and complete cytogenetic response, freedom from progression to accelerated-phase or blast-crisis CML, and tolerance of therapy, imatinib was significantly superior to interferon alfa plus low-dose cytarabine.

When the study was designed, the combination of interferon alfa and low-dose cytarabine was thought to be the most effective treatment for patients with newly diagnosed CML who were not considered candidates for allogeneic hematopoietic-cell transplantation.³⁰ Despite superior cytogenetic responses with the combination, improvement in survival has not been confirmed.³¹ Regardless, the results for the combination-therapy control group in our study (12-month rate of major cytogenetic response, 30.3 percent; and 12-month rate of complete cytogenetic response, 11.8 percent) are similar to those of a French study (39 percent and 15 percent, respectively)³⁰ and an Italian study (21 percent and 8 percent, respectively),³¹ and none ap-

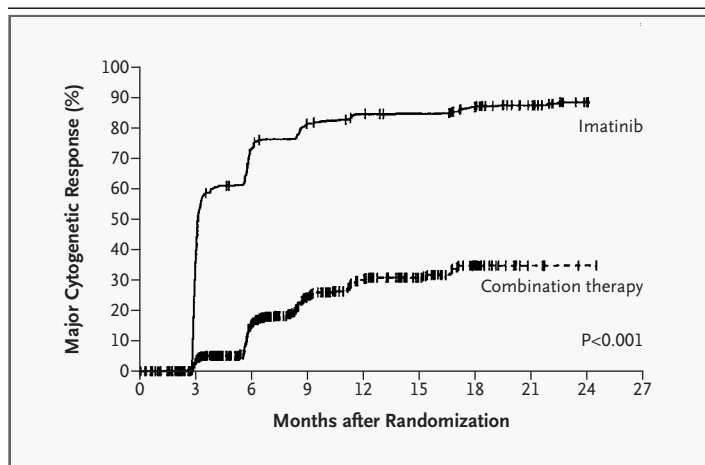


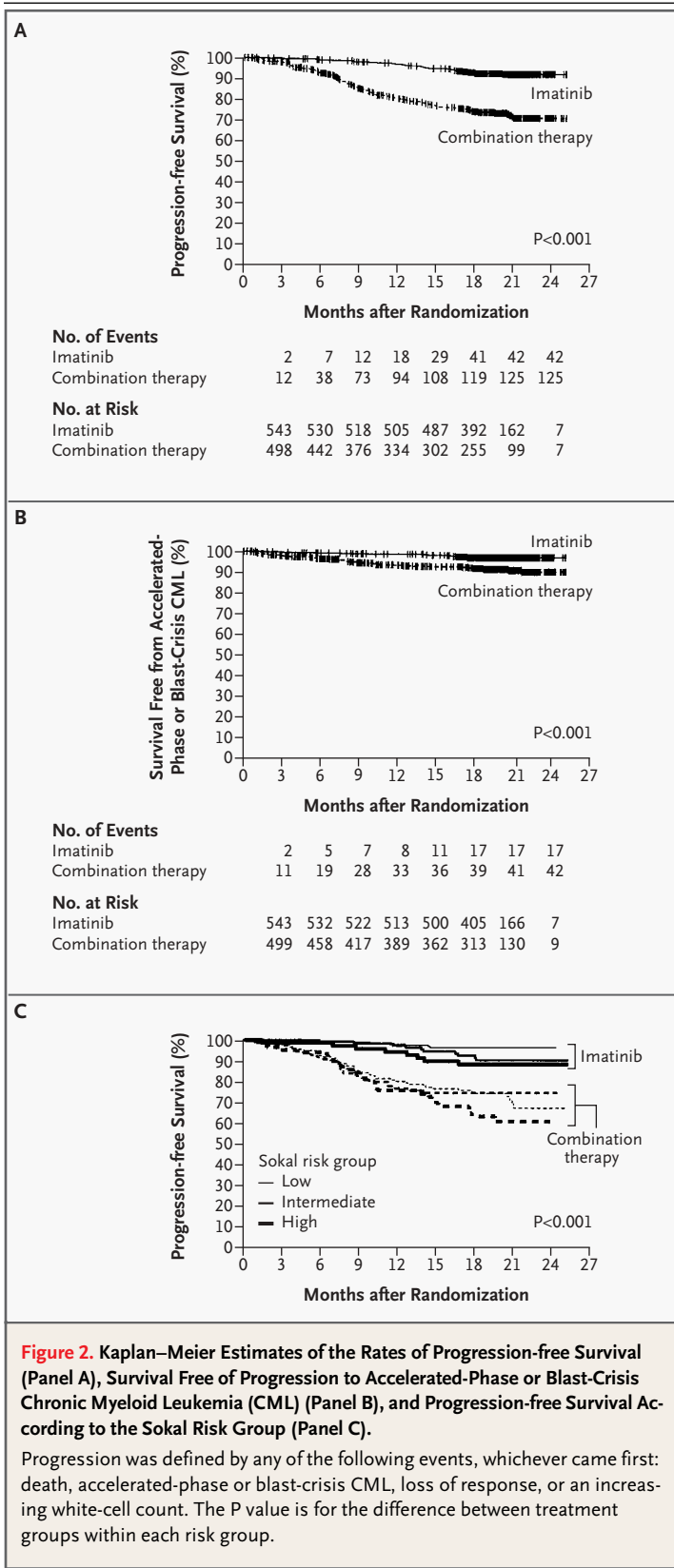
Figure 1. Kaplan–Meier Estimate of the Time to a Major Cytogenetic Response.

Data on patients who crossed over to the other treatment group or discontinued treatment for reasons other than progression were censored. At 12 months, the estimated rate of major cytogenetic response was 84.4 percent in the imatinib group and 30.3 percent in the group given interferon alfa plus low-dose cytarabine; the respective rates at 18 months were 87.1 percent and 34.7 percent.

proached the significantly better results achieved with imatinib.

Because of the favorable results of the phase 2 study of imatinib in late chronic-phase CML,²⁰ we considered a crossover design to be an essential element of the current study. Only 79 patients (14.3 percent) in the imatinib group discontinued the drug or crossed over to combination therapy, whereas 493 patients (89.2 percent) in the combination-therapy group did so. At the time of this analysis, 60 patients (10.8 percent) were still receiving combination therapy. Imatinib induced a complete hematologic response in 82.4 percent of patients who crossed over to this drug from combination therapy and induced a major cytogenetic response in 55.7 percent and a complete cytogenetic response in 39.6 percent. These results are similar to those of previous studies of imatinib in patients who had had no response to interferon alfa treatment: 95 percent had a complete hematologic response, and 60 percent had a major cytogenetic response (41 percent had a complete cytogenetic response).²⁰

Analysis of responses was complicated by the high rate of crossover and discontinuation of treatment. If response was analyzed only according to the first treatment received, our analysis may un-



derestimate the response to interferon alfa (compare Table 4 and Fig. 1). For example, a patient who crossed over to imatinib therapy because of intolerance might be counted as not having a response to combination therapy. To compensate for this possibility, we also analyzed the data using the Kaplan–Meier method, in which data on patients who crossed over or discontinued treatment for reasons other than progression were censored at the end of the initial treatment. In contrast, the use of a strict intention-to-treat principle may overestimate the rate of response and underestimate the rate of progression associated with interferon alfa therapy, since imatinib has been shown to be effective rescue therapy for patients who have no response to interferon alfa. We used the Kaplan–Meier method to estimate responses and a strict intention-to-treat principle to determine the rate of progression. Despite this conservative statistical approach, the differences remained large and significantly in favor of imatinib.

The outcome of patients whose disease has progressed to accelerated phase or blast crisis despite treatment with any therapy including imatinib³⁵ is significantly worse than the outcome of patients with chronic-phase CML. We found no demonstrable difference in survival between the two groups on an intention-to-treat basis, and it seems unlikely that any such difference will ever be observed. This is probably due to the early crossover of so many patients to the imatinib group. The study will continue for at least five years and will therefore allow us to determine the long-term outcome of imatinib therapy. However, taking into account the high rate of complete cytogenetic response and the early evidence of a delay in the progression to accelerated-phase or blast-crisis CML, we believe that imatinib therapy may significantly improve long-term survival.

The advent of imatinib already appears to have had an impact on the numbers of allografts being performed,³⁶ and the choice between drug therapy and transplantation for newly diagnosed CML is becoming increasingly difficult. A total of 52 patients have proceeded to transplantation so far, but it is not possible to make meaningful comments regarding their outcome, since the numbers are too small. On the basis of the high early mortality rate associated with bone marrow transplantation and the promising results with imatinib, early transplantation might be restricted to patients with the highest likelihood of success, such as younger patients

with matched sibling donors, and to patients with an insufficient response to imatinib.²³ We will continue to follow the patients in this study to evaluate the long-term tolerability of imatinib and the durability of responses and to determine whether the leukemia can be eradicated at the molecular level. Studies are under way to compare various doses of imatinib monotherapy with imatinib in combination with other agents.

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APPENDIX

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REFERENCES

- Nowell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. *Science* 1960;132:1497.
- Rowley JD. A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature* 1973;243:290-3.
- Bartram CR, de Klein A, Hagemeijer A, et al. Translocation of *c-abl* oncogene correlates with the presence of a Philadelphia chromosome in chronic myelocytic leukaemia. *Nature* 1983;306:277-80.
- Heisterkamp N, Stephenson JR, Groffen J, et al. Localization of the *c-abl* oncogene adjacent to a translocation break point in chronic myelocytic leukaemia. *Nature* 1983;306:239-42.
- Groffen J, Stephenson JR, Heisterkamp N, de Klein A, Bartram CR, Grosveld G. Philadelphia chromosomal breakpoints are clustered within a limited region, bcr, on chromosome 22. *Cell* 1984;36:93-9.
- Shtivelman E, Lifshitz B, Gale RP, Canaani E. Fused transcript of *abl* and *bcr* genes in chronic myelogenous leukaemia. *Nature* 1985;315:550-4.
- Lugo TG, Pendergast AM, Muller AJ, Witte ON. Tyrosine kinase activity and transformation potency of *bcr-abl* oncogene products. *Science* 1990;247:1079-82.
- Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the *P210bcr/abl* gene of the Philadelphia chromosome. *Science* 1990;247:824-30.
- Heisterkamp N, Jenster G, ten Hoeve J, Zovich D, Pattengale PK, Groffen J. Acute leukaemia in *bcr/abl* transgenic mice. *Nature* 1990;344:251-3.
- Kelliher MA, McLaughlin J, Witte ON, Rosenberg N. Induction of a chronic myelogenous leukemia-like syndrome in mice with *v-abl* and *BCR/ABL*. *Proc Natl Acad Sci U S A* 1990;87:6649-53. [Erratum, *Proc Natl Acad Sci U S A* 1990;87:9072.]

11. Elefany AG, Hariharan IK, Cory S. bcr-abl. The hallmark of chronic myeloid leukaemia in man, induces multiple haemopoietic neoplasms in mice. *EMBO J* 1990;9:1069-78.
12. Buchdunger E, Zimmermann J, Mett H, et al. Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative. *Cancer Res* 1996;56:100-4.
13. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med* 1996;2:561-6.
14. Buchdunger E, Cioffi CL, Law N, et al. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. *J Pharmacol Exp Ther* 2000;295:139-45.
15. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. *Blood* 2000;96:925-32.
16. Apperley JF, Gardembas M, Melo JV, et al. Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. *N Engl J Med* 2002;347:481-7.
17. Okuda K, Weisberg E, Gilliland DG, Griffin JD. ARG tyrosine kinase activity is inhibited by STI571. *Blood* 2001;97:2440-8.
18. Schindler T, Bornmann W, Pellicena P, Miller WT, Clarkson B, Kuriyan J. Structural mechanism for STI-571 inhibition of abelson tyrosine kinase. *Science* 2000;289:1938-42.
19. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001;344:1031-7.
20. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 2002;346:645-52. [Erratum, *N Engl J Med* 2002;346:1923.]
21. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med* 1999;340:1330-40.
22. Silver RT, Woolf SH, Hehlmann R, et al. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: developed for the American Society of Hematology. *Blood* 1999;94:1517-36.
23. Goldman JM, Druker BJ. Chronic myeloid leukemia: current treatment options. *Blood* 2001;98:2039-42.
24. Chronic Myeloid Leukemia Trialists' Collaborative Group. Interferon alfa versus chemotherapy for chronic myeloid leukaemia: a meta-analysis of seven randomized trials. *J Natl Cancer Inst* 1997;89:1616-20.
25. Allan NC, Richards SM, Shepherd PC. UK Medical Research Council randomised, multicentre trial of interferon-alpha n1 for chronic myeloid leukaemia: improved survival irrespective of cytogenetic response. *Lancet* 1995;345:1392-7.
26. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. Interferon alfa-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. *N Engl J Med* 1994;330:820-5.
27. Ohnishi K, Ohno R, Tomonaga M, et al. A randomized trial comparing interferon-alpha with busulfan for newly diagnosed chronic myelogenous leukemia in chronic phase. *Blood* 1995;86:906-16.
28. Hehlmann R, Heimpel H, Hasford J, et al. Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukemia. *Blood* 1994;84:4064-77.
29. The Benelux CML Study Group. Randomized study on hydroxyurea alone versus hydroxyurea combined with low-dose interferon-alpha 2b for chronic myeloid leukemia. *Blood* 1998;91:2713-21.
30. Guilhot F, Chastang C, Michallet M, et al. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. *N Engl J Med* 1997;337:223-9.
31. Baccarani M, Rosti G, de Vivo A, et al. A randomized study of interferon-alpha versus interferon-alpha and low-dose arabinosyl cytosine in chronic myeloid leukemia. *Blood* 2002;99:1527-35.
32. Sokal JE, Baccarani M, Russo D, Tura S. Staging and prognosis in chronic myelogenous leukemia. *Semin Hematol* 1988;25:49-61.
33. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. *J Natl Cancer Inst* 1998;90:850-8.
34. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
35. Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood* 2002;99:1928-37.
36. Gratwohl A, Baldomero H, Urbano-Ispizua A. Transplantation in chronic myeloid leukaemia. *Lancet* 2002;359:712-3.

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